Development of a theoretical model and preliminary evaluation of a self-management programme for different

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Development of a theoretical model and preliminary evaluation of a self-management programme for different types of pain in Multiple Sclerosis

by

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Abstract

Previous research indicates that many people with MS (pwMS) experience pain. Studies show that pain is associated with several potentially unhelpful psychosocial factors or processes, which may impact on pwMS' functioning and quality of life.

This thesis presents a series of studies outlining the development of a theoretical model of Multiple Sclerosis (MS) pain and a preliminary intervention to support pain management for pwMS.

Study 1: A systematic review of the literature proposed a cognitive behavioural model of MS pain showing that several psychosocial factors are associated with pain and related disability. A literature review of predominant theoretical models in chronic pain, their key constructs, empirical evidence, and treatment approaches, were shown to have comparable efficacy, and may potentially be relevant to pwMS.

Study 2: Following the literature reviews, a qualitative interview study exploring pwMS experiences of pain (n = 25) provided insights into pain-related beliefs, emotional reactions, disparate pain management attitudes and behaviours.

Study 3: A large quantitative cross-sectional questionnaire study of pwMS (n = 608) explored additional psychological factors, focusing on theory and gaps identified within the literature reviews. Cognitive and contextual behavioural variables explained substantial variance in pain and related functioning.

Study 4: The literature reviews, interviews and survey refined the MS pain model. This informed the development of a telephone supported hybrid cognitive and contextual behavioural self-management intervention aiming to alleviate the negative impact of pain in MS.

Study 5: A case series (n = 7) explored the potential efficacy of the self-management intervention for pwMS with different types of MS pain, showing mixed findings in pain outcomes and psychological process variables from the MS pain model.

This project has improved our understanding of MS pain, providing a potential tool that requires further evaluation, which may help pwMS better manage pain more effectively in the future.

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Abbreviations

Abbreviation	Meaning
ABCs	Antecedents, Behaviours and Consequences
AMB	Affective Memory Bias
ACT	Acceptance and Commitment Therapy
AE	Avoidance-Endurance Model of Chronic Pain
AEQ	Avoidance-Endurance Questionnaire Pain-related Behavioural Responses Scale
BDI	Beck Depression Inventory
BPI	Brief Pain Inventory
CBSQ	Cognitive and Behavioural Responses to Symptoms Questionnaire
CBT	Cognitive Behaviour Therapy
CCBT	Contextual Cognitive Behavioural Therapy
CES-D	Centre of Epidemiological Studies Depression Scale
CFQ	Cognitive Fusion Questionnaire
CMDI	Chicago Multidimensional Depression Inventory
CNS	Central Nervous System
CPAQ-8	Chronic Pain Acceptance Questionnaire 8 items
CPI	Community Participation Index
CPCI	Chronic Pain Coping Inventory
CSM	Common Sense Model of Illness Perceptions / Self-regulation
CSQ	Coping Strategies Questionnaire
CT	Cognitive Therapy
DER	Distress-Endurance Response
DMD	Disease Modifying Drugs
DN4	Douleur Neuropathique 4 Interview Questionnaire
EBV	Epstein–Barr-Virus
EDSS	Expanded Disability Severity Scale
EDSS-S	Expanded Disability Severity Scale Self-Report
EER	Eustress–endurance Response
FA	Fear-Avoidance Model of Chronic Pain
FACT	Focused Acceptance and Commitment Therapy
FSR	Pain related behaviour
GHQ-28	General Health Questionnaire
GIFT	Guided cognItive behavioural selF-management Treatment for MS pain
HADS	Hospital Anxiety and Depression Scale
HADS	Hospital Anxiety and Depression Scale
HCP	Health Care Professional
HQoL	Health-related Quality of Life
HSS	The Intensity of MS-related Headache Scale
HSV	Herpes simplex virus

IAPT	Improving Access to Psychological Therapies
IASP	International Association of the Study of Pain
ICHD-2	International Classification of Headache Disorders
IPQ-R	Illness Perceptions Questionnaire-Revised
IPQ-R	Illness Perception Questionnaire-Revised
KPI-AEM PCR	Kiel Pain Inventory Avoidance Endurance Questionnaire — Pain-related Cognitive Responses Subscale
MADRS	Montgomery and Asberg Depression Rating Scale
MBSR	Mindfulness-based Stress Reduction
MDS	Resident Minimum Dataset
MHI	Mental Health Inventory
MMPI	Minnesota Multiphasic Personality Inventory
MPQ/SF-MPQ	McGill Pain Questionnaire and Short Form Version
MPRCQ	Multidimensional Pain Readiness to Change Questionnaire
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSPSS	Multidimensional Scale of Perceived Social Support
MSSS	Medical outcomes Study Modified Social Support Scale
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NPS	Neuropathic Pain Scale
NPS-10	Neuropathic Pain Scale 10-items
NRS	Numerical Rating Scale
NS	Non-significant Parameters
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
PBPI	Pain Beliefs Perception Inventory
PCS	Pain Catastrophizing Scale
PES	Medical outcomes study Pain Effects Scale
PF	Psychological Flexibility Model
PHQ-9	Patient Health Questionnaire
PIR	Pain Interference Rating
PPI	MS Society Patient and Public Involvement Members
PPMS	Primary Progressive MS
PSWQ	Pennsylvania State Worry Questionnaire
PwMS	People with Multiple Sclerosis
QoL	Quality of Life
RCT	Randomised Controlled Trial
RET	Rational-Emotive Therapy
RFT	Relational Frame Theory
RRMS	Relapsing-Remitting Multiple Sclerosis
SDPS	Simple Descriptive Pain Scale
SEP-59	Self-administered quality of life questionnaire
SF-36	Short-Form 36-items quality of life questionnaire
S-LANSS	Self-report Leeds Assessment of Neuropathic Signs and

	Symptoms
SMA	Simulation Modelling Analysis
SNRIs	Serotonin–Norepinephrine Reuptake Inhibitors
SOPA	Survey of Pain Attitudes
SPMS	Secondary Progressive Multiple Sclerosis
SPSS	Statistical Package for the Social Sciences
STAI	State-Trait Anxiety Inventory
TENS	Transcutaneous Electrical nerve Stimulation
UVR	Ultraviolet Radiation
VAS	Visual Analogue Scale
WHOQOL-100	World Health Organisation 100

Chapter 1 : Providing a Context: Understanding Multiple Sclerosis (MS), its Psychosocial Impact and Current Evidence for Psychological Interventions.

1.1 Chapter overview

This first chapter will introduce the principal characteristics of Multiple Sclerosis (MS), outlining its pathophysiology, symptoms, phenotypes or courses, epidemiology, aetiology, diagnosis and current treatments. This will be followed by a brief account of the impact of MS, and a short review of psychological interventions developed specifically to manage psychosocial consequences and symptoms, including depression, adjustment and fatigue. An introduction to painful symptoms associated with MS, their negative impact, and a preliminary biopsychosocial model and psychological treatments will also be outlined. Finally, the chapter will conclude with a context and rationale for the programme of empirical research undertaken in this thesis.

1.2 Understanding Multiple Sclerosis

1.2.1 Pathophysiology, symptoms and classifications

1.2.1.1 Pathophysiology

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disease of the central nervous system (CNS) (Kingwell et al., 2013). MS is presumed to have an autoimmune pathogenesis (Sellner et al., 2011) in which the immune system becomes overactive, resulting in stripping and thinning of myelin sheaths that coat nerve fibres responsible for efficient transmission of nerve impulses. While MS has for a long time been regarded a demyelinating disease (Murray, 2006), recent evidence indicates a more complex interplay between several processes, including widespread inflammation (Confavreux, Vukusic, Moreau, & Adeleine, 2000), demyelination and re-myelination, glial cell loss and scarring, and neuronal and axonal degeneration (Compston & Coles, 2008). Whilst the order and relation of these processes remains unclear, over time they typically lead to an accumulation of lesions or sclerotic plaques in the nerves, resulting in irreversible disease progression and increased disability (Murray, 2006).

1.2.1.2 Symptoms

Since the CNS is primarily affected in MS, several areas in the body can potentially be affected. Whilst evidence suggests disease processes are present long before the first symptom (Murray, 2006), clinical manifestations show the involvement of sensory, visual, motor and autonomic systems (Compston & Coles, 2008). Specifically, classic neurological symptoms (or ‘signs’) include muscle weakness or spasms, blurred or double vision, and loss, or unpleasant distortions, of sensation (Samkoff & Goodman, 2011; Vollmer, Preiningerova, & Waxman, 2002). Fatigue, depression, and bladder dysfunction are the most commonly reported MS symptoms (Induruwa, Constantinescu, & Gran, 2012; Krupp, 2006; Minden et al., 2006), whilst others include pain, paraesthesia (tingling), hypoesthesia (numbness), cognitive impairment, balance disruption, and difficulties with speech and swallowing. However, a hallmark of MS is the considerable variability of neurological symptoms observed between individuals

(Vollmer et al., 2002), which can be acute or chronic in nature. Whilst correlations between cranial magnetic resonance imaging (MRI) and brain pathology are consistent, severity of relapses, changes in neurological status and symptoms, including fatigue and depression, are not associated with disease activity (Murray, 2006). Furthermore, there is now compelling evidence to suggest environmental factors, such as heat (Krupp, Alvarez, LaRocca, & Scheinberg, 1988) and certain types of stress are associated with worsening symptoms (Mitsonis, Potagas, Zervas, & Sfagos, 2009), even in the absence of new CNS injury (Vollmer et al., 2002).

1.2.1.3 Phenotypes

It is unclear whether MS represents one or several distinct diseases, since it can follow very different patterns of progression and variable rates of disability accumulation over several decades (Compston & Coles, 2008; Goldenberg, 2012). While several mechanisms have been proposed to explain the different pathogenesis of courses (Kremenchutzky, Rice, Baskerville, Wingerchuk, & Ebers, 2006; Lassmann, van Horssen, & Mahad, 2012), three major clinical phenotypes have been defined (Lublin & Reingold, 1996). Phenotypes include relapsing-remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS).

Around 85% of pwMS present with RRMS (Murray, 2006), which is described as an acute worsening of neurological functioning, followed by a variable degree of recovery, with a stable course between attacks (Lublin & Reingold, 1996). Some researchers have suggested the process of re-myelination may contribute to periods of partial or complete recovery for individuals with RRMS (Compston & Coles, 2008). However, over time around 65% of people with MS (pwMS) with RRMS enter the SPMS phase, characterised by uninterrupted progression with or without occasional relapses, minor remissions and plateaus (Lublin & Reingold, 1996). Whilst progressive disease typically begins around 40 years of age (Confavreux & Vukusic, 2006), 10% to 20% of pwMS may experience progressive illness from disease onset (Compston & Coles, 2008; Lassmann et al., 2012). Fifteen percent of pwMS present initially with PPMS (Murray, 2006), reflecting a gradual and almost continuously worsening baseline with minor fluctuations usually without relapses (Lublin & Reingold, 1996). Primary and secondary MS have been regarded as essentially similar (Compston & Coles, 2008; Confavreux & Vukusic, 2006).

There are two further MS categories that elude consensus in terms of an established clinical definition. A small number of pwMS are thought to experience "relapsing-progressive" MS (RPMS), characterised by a combination of relapse and progression (Bamer, Cetin, Amtmann, Bowen, & Johnson, 2007; Lublin & Reingold, 1996). In addition, around 15% of pwMS experience "benign MS", described as a 10 to 15 year period of minor symptoms or disability after a diagnosis, presumed to be a mild form of RRMS (Pittock et al., 2004).

The age of MS onset typically ranges from 20 to 45 years. Although MS often presents in middle age (Goldenberg, 2012), more recent evidence suggests around 3% to 10% of pwMS experience illness onset before 18 years of age (Mikaeloff, 2012). At 15 years post-diagnosis 80% of pwMS experience functional limitations, around 50% to 60% need assistance with ambulation, 70% are limited or unable to perform activities of daily living, and 75% are unemployed (Hauser & Oksenberg, 2006). Predictors of future disability in all MS subtypes include age of disease onset, sex (i.e. female), and extent of recovery after the first episode (Voskuhl & Gold, 2012). However, recent evidence shows that actual rates of disability accrual in pwMS with progressive disease vary considerably, where some experience long periods of clinical stability in absence of clinical worsening (Pandey et al., 2014). Despite the female preponderance in MS, men appear to have a poorer prognosis than women (Voskuhl & Gold, 2012). Whilst MS is not considered immediately fatal 50 to 60% of pwMS die from increased risk of infections, usually related to bladder, chest and skin complications at the more advanced stages of disease progression (Compston & Coles, 2008; Sadovnick, Eisen, Ebers, & Paty, 1991). The median time to death is around 30 years from disease onset, which equates to a reduction in life expectancy of 5 to10 years (Brønnum-Hansen, Koch-Henriksen, & Stenager, 2004).

1.2.2 Epidemiology and aetiology

1.2.2.1 Epidemiology

MS is the most common cause of neurological disability in young adults, and is estimated to affect around 2.1 million people worldwide, with approximately 175,000 newly diagnosed cases each year (WHO, 2008). According to more recent estimates 126,669 people were living with MS in the UK in 2010, and around 6000 new cases were diagnosed (Mackenzie, Morant, Bloomfield, MacDonald, & O'Riordan, 2014). Northern Europe is regarded a "high frequency zone" for MS (≥30/100,000), comprising over half of the population of people diagnosed across the globe (Kurtzke, 2000).

Epidemiological studies spanning the past six decades show incidence and prevalence estimates are higher in women compared to men (ratios ranging from 2:1 to 3:1, according to region), and recent meta-analyses indicate that the overall incidence of MS has increased over time, which is attributed to the increasing incidence among women (Duquette et al., 1992; Kingwell et al., 2013; Koch-Henriksen & Sørensen, 2010). Researchers propose several reasons why estimates have increased in the last few decades. Some argue the increase represents changes in heightened awareness and earlier detection, improved diagnostic techniques and longer survival (Compston & Coles, 2008; Koch-Henriksen & Sørensen, 2010; Ramagopalan & Sadovnick, 2011). Others suggest variation in study methods and quality, and a lack of diagnostic standardisation across geographic areas, may inflate current estimates (Kingwell et al., 2013; Poser & Brinar, 2007). However, it has been argued that increases in incidence cannot be attributed to advances in neuroimaging or changes in diagnostic criteria alone (Visser, Wilde, Wilson, Yong, & Counsell, 2012).

1.2.2.2 Aetiology: Genes and environmental factors

The causes or potential triggers of MS are not yet fully understood. However, it is widely accepted that a complex multifactorial interplay of genetic and environmental factors contribute to disease development (Almohmeed, Avenell, Aucott, & Vickers, 2013; Handel et al., 2011; Ramagopalan, Dobson, Meier, & Giovannoni, 2010; Vollmer

et al., 2002). Whilst there is evidence for a genetic risk component in MS (Compston & Coles, 2008), a large proportion of the disease heritability is still unaccounted for (Gourraud, Harbo, Hauser, & Baranzini, 2012). This may reflect limitations with genetic analyses, which often assume MS is one disease, when in fact there is evidence for genetic heterogeneity (Compston & Coles, 2008). Familial recurrence is around 20%, where first-degree relatives are most at risk (3%), and monozygotic (or identical) twins have five times the risk of developing the disease compared to dizygotic twins (25% vs. 5%). Consistent with the uneven geographic distribution of MS, prevalence rates vary substantially among different racial and ethnic groups, with the highest rates existing in Northern European Caucasians, and lowest in people of African or Asian origin (Vollmer et al., 2002).

A number of environmental risk factors have also been shown to determine susceptibility to MS and its disease course (Ebers, 2008; Koch, Metz, Agrawal, & Yong, 2013). The latitudinal gradient hypothesis suggests the global distribution of MS increases with greater distance north or south of the equator (Compston & Coles, 2008; Ramagopalan & Sadovnick, 2011), varying considerably between regions and populations, even when accounting for genetic factors (Simpson, Blizzard, Otahal, Van der Mei, & Taylor, 2011; Vollmer et al., 2002). The latitudinal gradient hypothesis and association between disease onset and migration from low- to high-risk regions before adolescence (Compston & Coles, 2008; O'Gorman, Lucas, & Taylor, 2012) has led researchers to examine evidence for the hygiene hypothesis (Leibowitz et al., 1966). The hygiene hypothesis assumes that a lack of exposure to childhood infections may predispose susceptible individuals to autoimmune and allergic diseases in later life (Fleming & Fabry, 2007). Therefore, Epstein–Barr virus (EBV), herpes simplex virus types 1, 2 and 6, measles, mumps and rubella have all been implicated as potential triggers of MS (Kakalacheva, Münz, & Lünemann, 2011; Vollmer et al., 2002). However, empirical support for the importance of viruses remains largely inconsistent. Whilst EBV in particular has received a lot of research attention more recently, studies examining the association between EBV and MS also show divergent results, and those examining causal relationships have several methodological limitations (Almohmeed et al., 2013; Ascherio & Munger, 2007; Kakalacheva et al., 2011; Koch et al., 2013). In addition, there is conflicting evidence for the association between MS and other autoimmune diseases (Compston & Coles, 2008).

More recently, inconclusive findings related to virus detection and infective agents have resulted in research examining environmental factors that vary with latitude. One of the most researched factors to date is ultraviolet radiation (UVR) or vitamin D (Simpson et al., 2011). Low exposure to sunlight, mediated through vitamin D insufficiency, appears to be associated with MS (Ho, Alappat, & Awad, 2012; O'Gorman et al., 2012; Ramagopalan & Sadovnick, 2011), and is regarded as a critical factor for the increasing incidence and prevalence of female cases (Sellner et al., 2011). Another potentially important environmental factor is cigarette smoking, which according to a recent meta-analysis, is associated with MS susceptibility in earlier life, although the effect on disease progression is less clear (Handel et al., 2011).

1.2.3 Diagnosis and treatment

1.2.3.1 Diagnosis

There is no single diagnostic test for MS (Goldenberg, 2012). Poser's diagnostic criteria emerged during the 1980s, requiring individuals to have at least two relapses or exacerbations typical of MS (time dissemination criterion), and evidence of disease involvement of white matter in more than one site in the CNS (space dissemination criterion) (Poser et al., 1983). McDonald's criteria later incorporated MRI findings to identify multiple areas of involvement, whilst examining patterns of change over time to detect new enhancing lesions (Fangerau et al., 2004; McDonald et al., 2001). A third criterion is chronic inflammation of the CNS, determined by analysis of cerebrospinal fluid with lumbar puncture procedures (inflammatory criterion) (Goldenberg, 2012). McDonald's criteria has improved diagnostic specificity and sensitivity (Murray, 2006; Pollmann & Feneberg, 2008), where the presence of one or more of these criteria allows for a general diagnosis of MS (Compston & Coles, 2008).

1.2.3.2 Treatment

Currently there is no cure for MS (Goldenberg, 2012; Ramagopalan & Sadovnick, 2011). However, advances in diagnostic techniques have enabled earlier decisions about pharmacological treatment options (Murray, 2006). Early treatments for pwMS included symptomatic therapies, supplemented by rehabilitation, exercise and diet (Vollmer et

al., 2002). The development of immunomodulatory or disease modifying drugs (DMDs) emerged in the 1990s (Compston & Coles, 2008), having a significant impact on altering the natural history of MS (Samkoff & Goodman, 2011). Early generalised immunosuppression DMDs included chemotherapies and corticosteroids. Whilst these have only demonstrated modest benefits in terms of slowing disease progression (Vollmer et al., 2002), they are often used to treat acute exacerbations to shorten the duration of MS attacks (Goldenberg, 2012).

A newer group of DMDs include beta interferon, an injectable therapy, which alters a class of immune system functions, irrespective of antigenic target, without causing generalised immunosuppression (Vollmer et al., 2002). A recent review indicates these drugs reduce relapses by one third and MRI-associated disease activity by 50% to 80% (Goldenberg, 2012), with effects persisting beyond two years of treatment (Duquette et al., 1995). Another treatment is an oral agent called glatiramer acetate, which alters immune response to a specific antigenic target (Vollmer et al., 2002). Three reviews suggest that large RCTs show newer DMDs reduce the severity and frequency of new demyelinating episodes (Compston & Coles, 2008; Lassmann et al., 2012; Murray, 2006). However, DMDs are only partially effective for people with RRMS and those with SPMS who continue to have relapses, but have very little benefit for those with PPMS (Compston & Coles, 2008; Goldenberg, 2012; Goodin, Cohen, O'Connor, Kappos, & Stevens, 2008). In addition, DMDs can potentially have unpleasant side effects (Goldenberg, 2012; Goodin et al., 2007) and do not lessen irreversible axonal injury, which is thought to account for the symptomatic burden of MS (Samkoff & Goodman, 2011). Therefore, treatment of MS-related symptoms aim to improve quality of life (Compston & Coles, 2008) and are regarded as an essential cornerstone of comprehensive care for pwMS (Boissy & Cohen, 2007). Pharmacological treatments have been used to manage several symptoms, including fatigue, bladder dysfunction, spasticity and mood, albeit with relative success (Compston & Coles, 2008). However, researchers suggest more difficult symptoms include pain and dysesthesia (abnormal sensation), motor problems, sexual dysfunction, weakness, tremor, ataxia (coordination and balance) and cognitive changes (Murray, 2006).

According to current National Institute for Health and Care Excellence (NICE) guidance for MS (NICE, 2003, 2014), in addition to the role of neurologists and pharmacological treatments, pwMS may also receive comprehensive care that includes

access to physiotherapists, occupational therapists, speech and language therapists, psychologists, social workers, pharmacists and continence specialists. These professionals provide expertise in the management of chronic neurological illness, with specialist nurse practitioners playing a key role in coordinating services and management for pwMS.

1.2.4 A Disease with high burden

A diagnosis of MS has profound social and psychological consequences for the individual, having the potential to threaten independence, autonomy, dignity and future plans (Boeije, Duijnstee, Grypdonck, & Pool, 2002; Vleugels et al., 1998). The onset of physical limitations associated with MS often occurs at a time when individuals are developing careers, building families or forming romantic relationships (Robinson, 1988). Evidence shows that symptoms and worsening disability may adversely affect several domains of functioning, placing limits on an individual's ability to work and generate an income, and engage in family and a broader social life. PwMS can also experience symptoms as embarrassing and unpredictable, which can be transient or invisible, resulting in the presence and seriousness of illness being doubted by others (Robinson, 1988). Quality of life (QoL), and physical and psychological domains of health-related quality of life (HQoL), defined as the capacity to derive satisfaction from meaningful behaviour despite disease (Benedict et al., 2005), are commonly associated with higher levels of fatigue, depression, physical disability and unemployment in MS (Aronson, 1997; Lobentanz et al., 2004; Miller & Dishon, 2006; Piwko et al., 2007; Rao et al., 1991). However, there is also a growing awareness that psychological, social and psychiatric issues influence HQoL in MS independent of physical disability (Mitchell, Benito-León, González, & Rivera-Navarro, 2005). Researchers have suggested that some pwMS appear to adapt well to modest disabilities, whilst others cope well even when faced with severe setbacks (Cruveilhier, 1998; Devins, Seland, Klein, Edworthy, & Saary, 1993).

MS also has a potentially negative impact on the wider social context. Although higher levels of social support are associated with greater QoL for pwMS (Schwartz & Frohner, 2005), poorer QoL in caregivers is associated with several factors, including being a spouse, caregiving for a long duration, greater severity of MS symptoms and disease subtype of the care recipient (Aronson, 1997). MS also has high costs for

society. Worsening disability in MS is associated with high health and social care costs and significant productivity losses in the UK (Kobelt, Berg, Lindgren, Fredrikson, & Jönsson, 2006; McCrone, Heslin, Knapp, Bull, & Thompson, 2008), Europe (Kobelt et al., 2006), Canada (Piwko et al., 2007) and the US (Zwibel & Smrtka, 2011). The overall cost of MS in the UK alone was estimated to be £1.5 billion in 1999, with a mean annual cost of over £30,000 per individual (Kobelt et al., 2000). Therefore, the negative consequences of MS are far-reaching, presenting an important challenge for health and social care providers worldwide.

1.2.5 Psychological consequences of MS and associated interventions

The literature highlights a variety of negative psychological consequences associated with MS. One review suggests that psychosocial factors are more strongly associated with reduced quality of life than disease variables (Mitchell et al., 2005). Since the 1980s psychological interventions have been developed to address some of these problems and have demonstrated promising efficacy. A brief summary of this research will be outlined in the following section, focusing on the specific contribution of cognitive behavioural treatments.

1.2.5.1 Cognitive behavioural therapy for depression and adjustment in MS

A common psychological consequence of MS is depression. Estimates of depression over the course of a person's lifetime range from 25% to 50%, which is 2 to 5 times greater than the general population, depending on the assessments used and the country studied (Feinstein, Magalhaes, Richard, Audet, & Moore, 2014; Ghaffar & Feinstein, 2007; Minden & Schiffer, 1990; Sadovnick et al., 1996; Siegert & Abernethy, 2005). Anxiety is not as well researched as depression in MS, but studies show that anxiety prevalence estimates range from 34% to 45% (Janssens et al., 2003; Korostil & Feinstein, 2007; Wood et al., 2012). Whilst recent longitudinal data suggests pwMS experience gradual reductions in anxiety over time (Wood et al., 2012), depression in MS is thought not to spontaneously remit (Mohr & Goodkin, 1999). Researchers have suggested that depression may be caused by a manifestation of cerebral inflammation, and a response to the uncertainties and restrictions imposed by the progressive and disabling nature of the condition (Compston & Coles, 2008). Depression has also been highlighted as a risk factor contributing to the 7.5 fold increase in suicide rates among

pwMS when compared to healthy controls (Sadovnick et al., 1991), with a cumulative lifetime risk of suicide from MS onset of 1.95% (Stenager et al., 1992) .

Five systematic reviews, including two meta-analyses, have summarised evidence for psychological interventions for depression and adjustment in MS (Hind et al., 2014; Mohr & Goodkin, 1999; Simpson et al., 2014; Thomas, Thomas, Hillier, Galvin, & Baker, 2006). Collectively, these reviews have predominantly focused on the efficacy of cognitive behavioural therapy (CBT), showing promising support for improved outcomes in pwMS. Broadly speaking, CBT is founded on the premise that physiological, cognitive (thinking), emotional, and behavioural responses may influence one another in a reciprocal way within the context of the social environment, where change in any one of these responses may produce changes in others (Beck, 1991; Dennison & Moss-Morris, 2010). The first review by Mohr et al (Mohr & Goodkin, 1999) included 5 studies showing that all treatments for depression in MS, including medication, stress management, insight-oriented therapy, and three studies evaluating CBT, were significantly more effective than no treatment, and comparable to antidepressant medication. A subsequent Cochrane review summarised rather limited trial evidence in this area, but concluded that CBT approaches may be beneficial in the treatment of depression and adjustment to MS (Thomas et al., 2006). The third review indicated that core components of CBT (i.e. goal setting and home work) were more beneficial in improving pwMS QoL compared to other non-pharmacological treatments (Malcomson, Dunwoody, & Lowe-Strong, 2007). A more recent meta-analysis of seven studies evaluating CBT for depression in MS showed a medium treatment effect size when compared to standard care and other alternative psychotherapeutic interventions (Hind et al., 2014). Overall, most of the reviewed studies have several methodological limitations, where many used small samples that were uncontrolled and non-randomised. However, a more recent clinical audit supports these efficacy-based trials, showing that CBT for depression and anxiety in routine clinical practice may be effective for pwMS (Askey-Jones, David, Silber, Shaw, & Chalder, 2013). Whilst CBT has been adapted for pwMS in these studies, few were guided by an empirically supported conceptual model of anxiety or depression specific to MS.

In contrast, there has been growing support for a theoretical model of adjustment that has guided treatment developments in MS. Adjustment has been variably defined in the context of chronic illness as “the healthy rebalancing by patients to their new

circumstances" (de Ridder, Geenen, Kuijer, & van Middendorp, 2008, p.246) or as affecting a range of life domains, unfolding over time and varying considerably between individuals (Stanton, Revenson, & Tennen, 2007). A large systematic review (Dennison, Moss-Morris, & Chalder, 2009), summarising evidence from 72 empirical studies, shows that several potentially modifiable cognitive behavioural factors, including perceptions related to illness, perceived stress and certain emotion-focused coping strategies, are associated with poorer outcomes across a number of domains in MS. These findings informed the development a conceptual model of MS adjustment (Dennison et al., 2009).

Briefly, the conceptual model of MS adjustment integrates elements within existing contextual and cognitive behavioural psychological models (Beck, 1976; Hayes, 1999). The model suggests that a person's previous learning history, and individual personality, influence the development of beliefs about one's self, the world or future (the cognitive triad). A person's beliefs are hypothesised to influence their behaviours, which includes their values and goals. However, critical events, including those specific to MS, such as receiving a diagnosis or experiencing new symptoms, relapse or disease progression, may interfere with pwMS' values, goals and behaviours. Consequently, a person's emotional equilibrium may become disrupted, posing a threat to their overall wellbeing and quality of life. Although emotional distress from the disruption is considered to be an expected response to critical events, the model suggests that prolonged distress may indicate problems with adjustment. The model identifies a variety of empirically supported cognitive behavioural factors or processes involved in this disruption process, which may interact and maintain distress. These include MS-specific illness representations or symptom perceptions, and related behavioural responses, such as excessive rest or avoidance of activities. The illness-specific nature of these cognitions and behaviours are distinct from more general beliefs (e.g. cognitive triad and threat perceptions) and behaviours typically addressed in the context of CBT for patients with anxiety and depression.

In combination with qualitative findings (Dennison, Yardley, Devereux, & Moss-Morris, 2010), a subsequent cross-sectional study of pwMS provided further support for the model of adjustment by showing that whilst disease factors, such as disease severity and MS subtype, accounted for around 25% of the variance in functional impairment, a further 20% was explained by cognitive and behavioural factors drawn from the model.

Specifically, behavioural responses to symptoms, including activity avoidance or excessive rest, and "all-or-nothing" behaviour, defined as over-exerting oneself when feeling well to meet perceived demands, resulting in periods where they need to rest and recover due to exhaustion, were identified as the strongest predictors of functional impairment. In addition, disease factors accounted for only 2.2% of the variance in distress, whilst cognitive and behavioural variables, including beliefs related to the self and how well pwMS understood their condition (coherence), accounted for a further 37%, in which self-related beliefs were the strongest predictors of distress (Dennison, Moss-Morris, Silber, Galea, & Chalder, 2010). The empirically supported model mapped directly onto the development of a nurse-led CBT intervention tailored specifically for MS adjustment (Moss-Morris et al., 2013). Whilst the intervention did not show significant treatment effects in functional outcomes and quality of life within the CBT (n = 48) compared to a supportive listening control group (n = 46), it did significantly reduce levels of distress for up to 12 months. Findings showed that the effect size observed in distress reduced from a moderate to small treatment effect from end of treatment to 12 months follow-up, which might be explained by the active ingredients of the supportive listening control group sharing some overlap with core components of CBT. There was also potential for aggregation bias, since pwMS with longer disease duration and greater levels of disability at baseline experienced larger decreases in quality of life. Overall, results indicate that a nurse led CBT treatment based on an empirically supported model of MS adjustment is likely to be helpful for pwMS.

To date, there has been a greater focus on using CBT for improving mental health and wellbeing in MS (Dennison & Moss-Morris, 2010), but less research has targeted the severity and impact of other MS symptoms traditionally viewed as 'somatic' in nature. However, a growing number of studies show that modifying psychological factors with CBT may improve management of other symptoms. A recent review including 22 studies indicates that whilst a variety of psychological interventions, including CBT, appear to reduce levels of depression and distress in MS, they also improve symptoms of fatigue, pain and insomnia (Pagnini, Bosma, Phillips, & Langer, 2014). However, to date few of these studies aimed to specifically target these symptoms, and only one has been guided by an empirically supported conceptual model of MS fatigue (van Kessel et al., 2008). A brief review of this work will now be summarised.

1.2.5.2 A conceptual model and cognitive behavioural treatment for MS fatigue

Fatigue is one of the most prevalent and disabling MS symptoms (Krupp et al., 1988; Monks, 1989), having the potential to limit a person's ability to carry out everyday activities, and result in unemployment and reduced quality of life (Amato et al., 2001; Bol, Duits, Hupperts, Vlaeyen, & Verhey, 2009). Whilst current biomedical treatments for fatigue demonstrate modest efficacy (van Kessel et al., 2008), a larger body of MS empirical studies (Bol et al., 2009) and a conceptual model of MS fatigue (van Kessel & Moss-Morris, 2006) suggest that biological, emotional, cognitive and behavioural factors play a potentially important role in the maintenance of this multifactorial symptom. Whilst disease inflammation and demyelination are thought to trigger fatigue, cognitive behavioural factors such as anxiety, depression, helplessness, emotional representations (i.e. the extent to which the fatigue affects them emotionally), and beliefs surrounding fatigue, related to somatic or causal attributions, consequences, timeline (i.e. how long the person believes the fatigue will last), control and coherence (i.e. the extent the person believes that they understand their fatigue) are consistently associated with worse fatigue severity and related disability (Bol et al., 2009; Jopson & Moss-Morris, 2003; Knoop, van Kessel, & Moss-Morris, 2012)[1]. In addition, findings indicate that specific behavioural responses may also result in greater fatigue and disability. Specifically, pwMS may either engage in excessive rest or avoid activity (both forms of behavioural avoidance), or "all-or-nothing" behaviour (Skerrett & Moss-Morris, 2006). The model suggests that these responses contribute to the maintenance of worsening fatigue, distress, and disability over time (see example in Figure 1 below).

[1]For more details on the theory that underpins these psychological variables see Leventhal's Common Sense Model of Illness Perceptions outlined in chapter 2 section *2.3.2.3* (Leventhal, Brissette, & Leventhal, 2003).

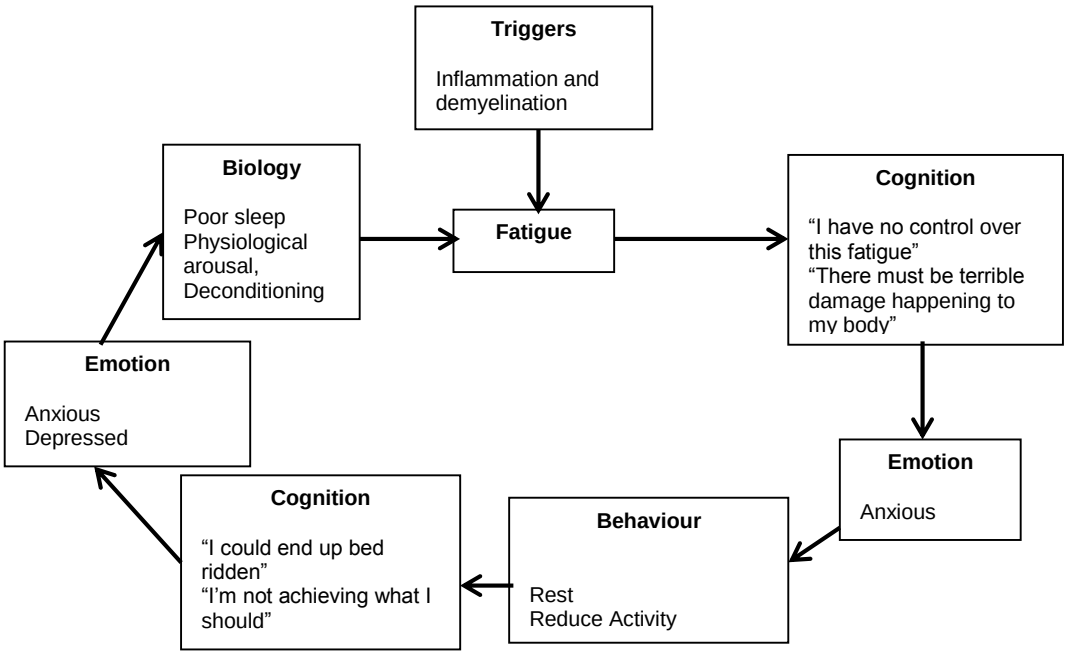

Figure 1: An example of cognitive and behavioural factors involved in of MS Fatigue (van Kessel & Moss-Morris, 2006)

There have also been a number of psychological interventions designed to address improved fatigue management in MS. One recent scoping review (Asano, Berg, Johnson, Turpin, & Finlayson, 2014) and two systematic reviews (Asano & Finlayson, 2014; Khan, Amatya, & Galea, 2014) show that non-pharmacological interventions, including CBT, are more effective in reducing fatigue and its impact compared to current pharmacological treatments. However, only two of the reviewed studies evaluated CBT programmes specifically targeting factors in the MS fatigue model outlined above to improve fatigue management (Moss-Morris et al., 2012; van Kessel et al., 2008). Both studies also indicated that CBT was substantially more effective in these studies compared to other reviewed educational or psychological interventions.

One of the studies was an RCT, which compared an eight-week manualised CBT programme tailored specifically for MS fatigue (n = 35) to relaxation training (n = 37). The study showed that both treatments were clinically effective in reducing fatigue to levels of a healthy comparison group, and these large significant effects were maintained at six months follow-up (van Kessel et al., 2008). Whilst there were no significant differences between the treatment groups on secondary outcomes, there were trends of improvement in fatigue-related impairment in both groups, and greater reductions in anxiety, depression and perceived stress within the CBT group. Therefore,

one potential limitation is that these findings may reflect non-specific treatment factors, including pwMS' expectations, along with support and therapist time and attention common to both approaches (van Kessel et al., 2008). However, a secondary data analysis provided additional support for the MS fatigue model, where avoidance behaviour and cognitive variables, including symptom focusing, believing symptoms were a sign of damage, and negative illness perceptions of fatigue, mediated treatment effects, showing that change in these factors predicted the greater improvement in the CBT compared to the relaxation group (Knoop et al., 2012).

The second study was a smaller pilot RCT, which evaluated the feasibility, efficacy and cost-effectiveness of a web-based version of the same MS fatigue intervention. Findings showed that pwMS receiving online CBT (n = 23) showed significantly greater improvements in anxiety and depression, and quality-adjusted life years compared to standard care (n = 17) (Moss-Morris et al., 2012). Furthermore, another recent pilot RCT, which was not included in the reviews outlined, used the online elements of the self-management intervention only (van Kessel, Wouldes, & Moss-Morris, 2015). Findings demonstrated that pwMS who received online CBT with email support (n = 19) had significantly greater reductions in fatigue severity and impact compared to those without email support (n = 20). Overall, these findings provide further evidence for the proposed cognitive behavioural model of MS fatigue (van Kessel & Moss-Morris, 2006), and suggest that low and high intensity tailored CBT interventions mapping directly onto the model of MS fatigue, may be clinically, and potentially cost-effective, treatments. However, larger pragmatic RCTs evaluating both clinical- and cost-effectiveness are needed before firm conclusions can be drawn. Research on MS fatigue has parallels with research in chronic pain, which is conceptualised using biopsychosocial and cognitive behavioural models (these will be discussed in greater detail in chapter 2). However, there has been little work in this area focusing specifically on troublesome or disabling pain in MS.

1.2.6 The problem of pain in MS

1.2.6.1 Prevalence and aetiology

A recent meta-analytic review suggests that pain affects around 63% of pwMS (Foley et al., 2013). However, many studies report variable prevalence estimates, which may in part be due to divergent definitions of pain, measurements used and patient populations studied (Alschuler, Jensen, & Ehde, 2012b; Michalski, Liebig, Thomae, Hinz, & Bergh, 2011; O'Connor, Schwid, Herrmann, Markman, & Dworkin, 2008). MS associated pain is not a single symptom, but rather reflects a number of complex syndromes arising from multiple aetiologies (Osborne, Jensen, Ehde, Hanley, & Kraft, 2007). Whilst a review of neuroimaging studies has identified positive associations between the location of demyelinating lesions and specific neuropathic pain syndromes in MS, neuro-radiological correlates of pain are generally small (Seixas et al., 2014). Therefore, the precise underlying biological mechanisms of painful syndromes in MS remains unclear, and causal distinctions related to chronicity used in the literature may not necessarily be accurate (Seixas et al., 2014). PwMS can experience acute or chronic pain (Indaco, Iachetta, Nappi, Socci, & et al., 1994), which is broadly classified as either neuropathic pain, resulting from nerve damage due to the underlying pathological process (Beard, Hunn, & Wight, 2003), musculoskeletal pain, related to degenerative muscle or joint dysfunction, usually secondary to spasticity, mobility, or gait and posture anomalies (Grasso et al., 2008). PwMS may also experience migraine headache (O'Connor et al., 2008), which may be neuropathic in origin, or unrelated or secondary to disease processes (Moisset et al., 2013). Pain may also be caused by other MS symptoms and treatments (Pöllmann, Erasmus, Feneberg, Bergh, & Straube, 2002; Pollmann & Feneberg, 2008). Neuropathic pain includes central neuropathic (‘‘dysesthetic’’) extremity pain (described as burning sensations in the limbs), trigeminal neuralgia (facial pain), Lhermitte's sign (a sudden electric shock-like sensations in the neck, which spreads to the arms or legs, usually triggered by flexion in the neck, bending forward, coughing or sneezing), and painful tonic spasms, including paroxysms (MS Society UK, 2011). One review suggests the most common form of pain in MS is central dysesthetic extremity pain (O'Connor et al., 2008). However, pwMS usually experience one or more of these painful symptoms over the course of their disease (Pollmann & Feneberg, 2008).

Several demographic and disease factors appear to be associated with a greater likelihood of painful symptoms in MS. These include older age, longer disease duration, and greater disease severity, where people with progressive MS have a greater risk of developing pain compared to other MS subtypes (O'Connor et al., 2008). Whilst other studies suggest the presence of MS pain is not consistently associated with age or gender (Archibald et al., 1994; Beiske, Pedersen, Czujko, & Myhr, 2004; Ehde et al., 2003; Stenager, Knudsen, & Jensen, 1991), women tend to report greater intensity or severity of pain (Hadjimichael, Kerns, Rizzo, Cutter, & Vollmer, 2007). Since there are no reliable biomarkers of pain in MS, pain severity has been operationalised in clinical and research settings using subjective self-report instruments. Whilst instruments can vary in the literature, pain severity is commonly measured using numerical rating scales (NRS), which can either range from 0 (no pain) to 10 (pain as bad as you can imagine) or 0 to 100, or visual analogue scales (VAS). Recent efforts to categorise pain experience using 0 to 10 point NRS suggest that MS pain can be classified as mild, moderate or severe (Alschuler et al., 2012b). One of the largest MS pain studies in the literature (n = 7579) indicates that greater pain severity is associated with lower educational level, increased age and disability, and an unstable disease course (Hadjimichael et al., 2007).

1.2.6.1 The impact of MS pain

MS pain is directly associated with reduced QoL and HQoL in MS (Mitchell et al., 2005; O'Connor et al., 2008). Pain severity is also related to reduced physical functioning and role limitations (Brochet et al., 2009; Kalia & O'Connor, 2005; Newland, Naismith, & Ullione, 2009), and increased pain interference (Bruce & Arnett, 2009; Glowacka, 2010; Hirsh, Turner, Ehde, & Haselkorn, 2009). Alschuler et al's classification system for pain severity in MS was developed in conjunction with measures of pain interference (Alschuler et al., 2012b), reflecting another key outcome within chronic pain trials (Dworkin et al., 2010; Dworkin et al., 2008). Pain interference has been defined as the extent to which pain interferes with every-day life activities, including sleep, mood, mobility, relationships and recreational activities (Ehde, Osborne, Hanley, Jensen, & Kraft, 2006; Osborne, Raichle, Jensen, Ehde, & Kraft, 2006). Pain-related interference is also typically measured using NRS ranging from 0 (does not interfere) to 10 (completely interferes), across these different life domains.

There are mixed findings for the relationship between the presence of pain and unemployment status in MS (Julian, Vella, Vollmer, Hadjimichael, & Mohr, 2008; Miller & Dishon, 2006; Newland, Fearing, M., & Neath, 2012; Simmons, Tribe, & McDonald, 2010), but longitudinal evidence suggests pain does not appear to predict unemployment over time (Julian et al., 2008). However, several studies show that pwMS with greater pain severity tend to report higher levels of disability and make more health care visits than those without pain (Alschuler, Jensen, & Ehde, 2012a; Hadjimichael et al., 2007; Khan & Pallant, 2007; Sullivan, Edgley, Mikail, Dehoux, & et al., 1992). A recent cross-sectional study in the US indicates that 75% of pwMS report at least one visit to their healthcare provider for pain within a 6 month period, with an average of 9.7 visits per person (Ehde, Alschuler, et al., 2015), which indicates pain may be inadequately treated and is associated with high healthcare costs.

The majority of existing MS studies show that pain is associated with impaired psychosocial functioning (Douglas, Wollin, & Windsor, 2008; Ehde et al., 2006; Grasso et al., 2008; Hirsh, Bockow, & Jensen, 2011; Hirsh et al., 2009; Khan & Pallant, 2007), and is related to increased rates of depression (Alschuler, Ehde, & Jensen, 2013; Brochet et al., 2009; Hadjimichael et al., 2007; Newland et al., 2009; White, White, & Russell, 2008) and anxiety (Bruce & Arnett, 2009; Kalia & O'Connor, 2005; Rog, Nurmikko, Friede, & Young, 2007; White et al., 2008). This is consistent with the finding that pwMS also view pain as one of the most distressing MS symptoms (Kalia & O'Connor, 2005).

1.2.6.2 Current treatments

Recent studies indicate the most common treatments for pain reported by pwMS are biomedical or biomechanical in nature, including pharmacological therapies, physical therapies, stimulation techniques and surgical interventions (Ehde, Alschuler, et al., 2015; Jensen & Finnerup, 2007; Khan & Pallant, 2007). According to a recent US study, pwMS have access to a range of drug treatments for pain (Ehde, Alschuler, et al., 2015). Anticonvulsants and tricyclic antidepressants are typically prescribed for neuropathic pain (Jensen & Finnerup, 2007; Kalso, Aldington, & Moore, 2013), whilst other drug classes include non-steroidal anti-inflammatory drugs (NSAIDS), acetaminophen, serotonin–norepinephrine reuptake inhibitors (SNRIS), opioids, cannabinoids, compound analgesics, local anesthetics, triptans, benzodiazepines,

benzoxazocine, benzcycloheptenes, and capsaicinoids. Whilst certain pharmacotherapies for pain have known mechanisms of action, researchers in the area concede that it can be difficult to determine the specific underlying causal mechanisms for each patient (Jensen & Finnerup, 2007). Four reviews show that pharmacological treatments for MS pain range in their effectiveness depending on the medication evaluated (Beard et al., 2003; De Santi & Annunziata, 2012; Jawahar, Oh, Yang, & Lapane, 2013; Siniscalchi, Gallelli, & De Sarro, 2007). However, few drug treatments have been examined within RCTs, and generally there is insufficient evidence to support their efficacy despite some being well-established in the clinical context. Another limitation cited in these reviews is the lack of consistency of pain severity and other outcome measures across studies (Beard et al., 2003).

One recent cross-sectional study suggests that some pwMS report benefits from biomedical treatments, achieving around 30% to 60% of pain relief from a range of medications, including non-prescribed smoked marijuana (Ehde, Alschuler, et al., 2015; Khan & Pallant, 2007). However, other studies indicate MS pain is often described as pervasive and overwhelming (Douglas, Windsor, & Wollin, 2008), and the majority of individuals experience persistent pain that is poorly controlled (Kerns, 2000). Therefore, it is not surprising that pwMS can often feel dissatisfied with their doctor's efforts to manage their pain (Hadjimichael et al., 2007). Consistent with these findings, one cross-sectional study shows that 45% of pwMS rated pain medications as the most *effective* treatment, but 48% felt they were *ineffective* (Heckman-Stone & Stone, 2001). It is also evident that most drug treatments for MS pain appear to have unpleasant side effects, including tiredness, interrupted sleep, nausea, diarrhoea, seizures and physical dependence (Siniscalchi et al., 2007; Smith, 2007; Wade, Makela, House, Bateman, & Robson, 2006), and some pwMS may fear the use of analgesics and prefer to avoid them (Abe et al., 2008).

There is also a range of physical treatments for MS pain, although to date few have been carefully evaluated in the context of RCTs. Physical treatments include strengthening exercises, physical therapy, massage, pressure, heat or ice, whirlpool, mobility or range of motion exercises, change in position, change of clothes, comfortable furniture, chiropractic care, acupuncture, electric vibration, and nerve blocks (Ehde, Alschuler, et al., 2015; Khan & Pallant, 2007). According to a recent review (Jawahar, Oh, Yang, & Lapane, 2014), one potentially useful physical treatment is transcutaneous electrical

nerve stimulation (TENS), which has shown clinically, but not statistically, significant reductions in pain severity in two studies (Al-Smadi et al., 2003; Warke, Al-Smadi, Baxter, Walsh, & Lowe-Strong, 2006). However, only one of these studies was an RCT, and TENS effects tend to be short-term and only suitable for pwMS with chronic low back pain. Overall, whilst 44% of pwMS report using physical therapies (Khan & Pallant, 2007), most report achieving anywhere between 38% to 67% of pain relief (Ehde, Alschuler, et al., 2015). The variability in these findings is consistent with a recent systematic review of 13 studies showing that some non-pharmacological treatments, may reduce non-spastic and non-trigeminal central neuropathic pain severity (Jawahar et al., 2014). However, these studies focused primarily on pain severity and not pain-related functioning, and support for educational and physical interventions was mostly inconclusive due to a lack of RCTs evaluating their efficacy. Therefore, whilst educational, drug and physical treatments appear to have some benefit, it may be that offering pwMS an additional approach, alongside these treatments, may reduce pain severity and improve self-management and pain-related functioning.

1.2.6.3 Preliminary biopsychosocial model of MS pain and psychological intervention research

Compared to the primary chronic pain literature (see chapter 2), the psychosocial aspects of MS pain have received far less research attention to date, although there are studies examining the role of psychosocial factors in MS pain (see systematic review Harrison, McCracken, et al., 2015 in chapter 3). However, the majority of these studies have investigated psychosocial variables in isolation, and were not guided by a conceptual model that explains how these factors may contribute to pain severity and related disability, and how they interact with the neurobiology underpinning pain.

One biopsychosocial conceptualisation of MS pain has been proposed in the literature (Kerns, 2000; Kerns, Kassirer, & Otis, 2002). Based on the diathesis stress model, this conceptualisation proposes that MS pain is multidimensional. Specifically, it suggests that in addition to neurobiological factors (including genetics), a person's predisposing characteristics or vulnerabilities, learning history or life circumstances, will also influence their cognitive, emotional and behavioural responses to the stress associated with the challenges of pain and MS. Kerns also highlights how a person's social context, including interactions with others, and observations of their behaviour (i.e.

social learning theory), may also influence how well they adapt to pain. Importantly, the model emphasises that all dimensions have equal importance in contributing to pain experience and functioning, which together determine an individual's adjustment. Kerns' model is therefore consistent with the diathesis stress theory of chronic pain, which suggests that when pain affects an individual who is already under significant psychological strain, or whose coping resources are already over-stretched, this may result in greater functional limitations and lead to higher levels of emotional distress (Flor, 2007; Linton & Shaw, 2011). However, an important adaption of Kerns' model was that is recognised neurobiological factors specific to MS that may contribute to pain experience (e.g. disease status, relapse and pain medications), and highlighted the dynamic nature of a person's adjustment in response to changing symptoms and disease progression. A key strength of the model is that it clearly identifies the need to examine the role of neurobiological variables specific to MS pain, including disability status, mental status, MRI findings and medication use, in conjunction with psychosocial elements.

Kerns' diathesis stress model also has some limitations. First, the model is more global in nature and fails to provide the content specificity of chronic pain models outlined in chapter 2 (Hasenbring & Verbunt, 2010; McCracken & Morley, 2014; Turk, Meichenbaum, & Genest, 1983; Vlaeyen & Linton, 2000). Specifically, the model predominantly focuses on pwMS' predisposing vulnerability factors, which in combination with disease or pain-related stress, determines their perceived ability to cope with pain and its consequences (i.e. appraisals of coping efficacy), ultimately influencing the way in which they respond to pain. However, the model does not outline the specific cognitive or behavioural responses described in existing chronic pain theories, such as viewing pain as chronic or as a sign of damage, which may lead to excessive rest or over-exertion avoidance behaviours. In addition, it does not explain how these psychosocial factors interact with each other or neurobiological aspects. Consequently, the model does not distinguish between those psychosocial factors or processes that may be more or less helpful in this context. Therefore, it reflects a more broad-brush model that provides limited understanding of pwMS' specific cognitive and behavioural responses to pain, and therefore offers limited guidance on how to intervene with cognitive behavioural treatments. Another limitation relates to review findings showing that neuropathic pain is relatively common in MS (O'Connor et al., 2008). Whilst Kerns highlights the importance of neurobiological factors, the model does not

explicitly distinguish between neuropathic and non-neuropathic (musculoskeletal) pain subtypes, which may lead to different psychosocial responses. Overall Kerns' adaption of the diathesis stress model is a useful way of understanding MS pain because it emphasises interactions between a broad range of biological and psychosocial elements (Dworkin & Banks, 1999). Therefore, the model has been helpful in highlighting that MS pain has mainly been considered from a biomedical perspective, and a shift towards a broader biopsychosocial model is now needed.

Another model in the MS literature draws on the motivational model of pain self-management initially proposed by Jensen, Nielson and Kerns (see Figure 2) (Jensen, Nielson, & Kerns, 2003). In contrast to Kerns' global conceptualisation, this model focuses more on the motivational dimension of pain, emphasising that a person's pain experience will depend, to a large extent, on how they choose to cope with pain and its impact. Specifically, it suggests that a person's readiness to change (or maintain) more adaptive self-management behaviours, and avoid maladaptive responses, is influenced by their beliefs about the importance of coping behaviours and their ability to successfully perform them (i.e. self-efficacy). In turn the person's behavioural coping responses are assumed to influence their overall functioning. The model has recently been empirically tested in the context of MS (Kratz, Molton, Jensen, Ehde, & Nielson, 2011). Consistent with other chronic pain populations (Molton, Jensen, Nielson, Cardenas, & Ehde, 2008), findings indicated that perceived importance and self-efficacy beliefs about coping were not directly related to pwMS' engagement with self-reported exercise or task persistence self-management behaviours. However, the relationship between both perceived importance and self-efficacy, and self-management behaviours was mediated by the person's readiness to engage in those behaviours. As with other chronic pain models outlined in chapter 2, a key strength of the motivational model of pain is that it provides greater content specificity in terms of motivational processes. These constructs can therefore be empirically tested and targeted in the context of psychological interventions. Another strength of this model is that psychological constructs investigated map directly onto clinical approaches in the broader field of psychology, such as motivational interviewing (Miller & Rollnick, 2002), which can be incorporated within CBT treatments.

The motivational model of pain self-management also has several limitations. First, the model has a narrower motivational focus, since it only includes pwMS' beliefs about the

importance of engaging in pain management behaviours, and their ability to perform them successfully. The emphasis on motivation therefore appears to be to the exclusion of other potentially important cognitive factors or processes and emotional responses outlined in chronic pain theories in chapter 2. In addition, the model fails to acknowledge the role of neurobiological variables outlined in Kerns' conceptualisation (Kerns et al., 2002). Therefore, the model may not be broad enough to explain the role of other potentially important psychological factors or processes associated with MS pain reviewed in chapter 3. Second, it is less clear whether self-management behaviours in the model are necessarily maladaptive or adaptive. For example, recent theories in chronic pain would argue that adaptive behaviours in the motivational model, such as ignoring pain, or persisting with tasks, could actually reflect potentially unhelpful behaviours in some circumstances (Eccleston & Crombez, 2007; Hasenbring & Verbunt, 2010; McCracken & Morley, 2014). Conversely, asking others for assistance when experiencing pain may not always be a maladaptive response. Another related issue is that the primary chronic pain literature generally regards pain severity and pain interference as important outcomes in all chronic pain trials (Dworkin et al., 2008). However, the primary outcomes identified in the motivational model of pain self-management is coping behaviour, which is variably defined as behaviours or cognitions that are hypothesised to reflect either adaptive or maladaptive coping responses (Jensen et al., 2003). Therefore, the motivational model of pain self-management fails to specify which outcomes are of key importance, and does not explain how psychosocial variables interact with pain severity and pain interference outcomes, or neurobiological factors specific to MS. A final point is that the model specifies directionality by suggesting that cognitive factors influence coping responses. However, Kratz et al (Kratz et al., 2011) do not clearly explain how these factors may interact in a reciprocal way to maintain pain and related disability in MS over time.

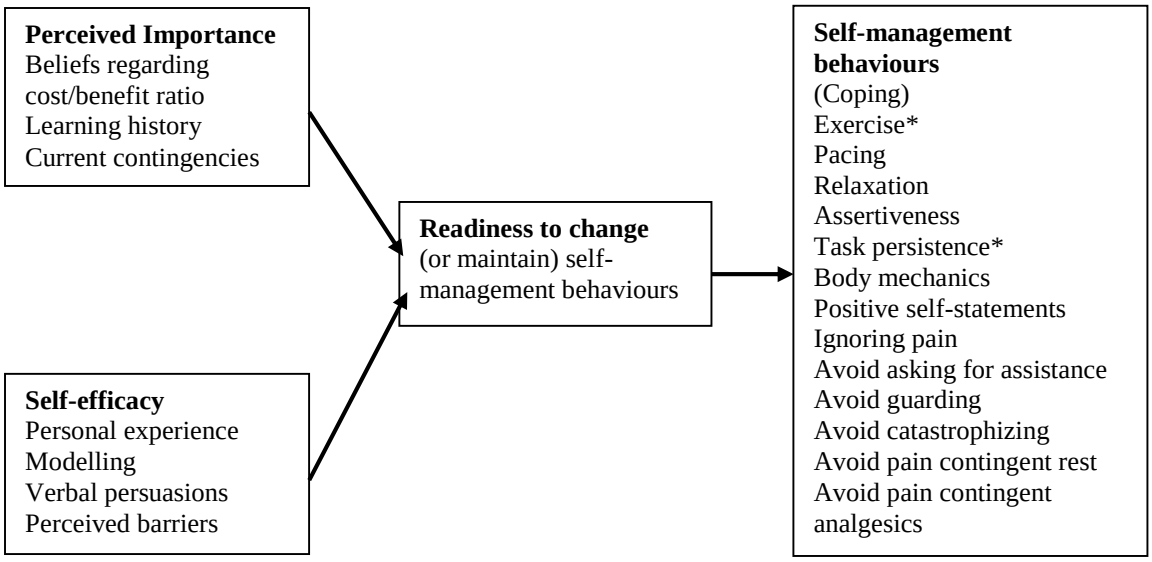

Figure 2: The motivational model of pain self-management (Kratz et al., 2011)

A more recent study has also proposed a biopsychosocial model of MS pain by examining associations between pain severity, other MS symptoms, depression and social support (Day et al., 2015). Consistent with a similar MS study (Shahrbanian, Duquette, Ahmed, & Mayo, 2015), findings indicate that most of these variables were significantly correlated with pain severity. However, the path-analytic model outlined was not explicitly linked to any established psychological theory, and focused mostly on depression to the exclusion of other potentially modifiable cognitive behavioural variables identified in existing chronic pain theories.

In summary, whilst a few theories of MS pain have been proposed they all have some limitations, and most fail to review models in light of existing empirical evidence. It might therefore be useful to learn from more established chronic pain research spanning over the past fifty years to understand if specific psychosocial constructs from chronic pain theories can explain pain in MS. This large body of research might be helpful for explaining pwMS' experience of non-neuropathic (musculoskeletal) pain in particular. However, it may also be helpful to explore the relevance of primary chronic pain models to improve our understanding of neuropathic pain.

1.3 Thesis rationale and overview

The current thesis aims to develop a conceptual model to guide the design and evaluation of a treatment to support pain management for pwMS. The empirical studies conducted in this thesis aimed to improve our understanding of MS pain and provide a potential intervention to assist pwMS to better manage this symptom in the future.

To enhance our conceptual understanding of MS pain, literature describing the predominant theoretical models, key constructs, empirical evidence, and treatment approaches and their efficacy, in the context of chronic pain is reviewed and critiqued in chapter 2. This is followed by a brief summary of how these approaches may be relevant to MS pain. In chapter 3, a systematic review of studies investigating potentially modifiable psychosocial factors and processes associated with pain severity and pain related interference in MS was conducted (published article, *Psychosomatic Research*)[2]. The review findings contributed to the development of a preliminary cognitive behavioural theoretical model of MS pain. The following two chapters used different methods to test and refine the theoretical model of MS pain developed from the review. Chapter 4 presents a qualitative interview study using thematic analysis exploring key themes in experiences of pain in MS (published article, *Multiple Sclerosis Journal*). Chapter 5 describes a large quantitative cross-sectional questionnaire study of pwMS exploring associations between cognitive, emotional and behavioural variables drawn from the model, and pain severity and pain interference (published article, *European Journal of Neurology*). Chapter 6 summarises the development of a self-management intervention for MS pain, and how it links to the updated cognitive behavioural theoretical model. A recently submitted article summarising individual case-series using mix-methods to evaluate the potential efficacy of an eight-week self-management intervention with telephone support aiming to reduce pain severity and pain-related interference in pwMS is then presented in chapter 7. An examination of key processes of change in this study enabled further refinement of the theoretical model. Finally chapter 8 includes a discussion of findings and limitations across the studies included in the thesis, providing directions for future research.

[2]All citations within published articles have been converted to APA 6th style and will be included in the final reference section of the thesis.

Chapter 2 : Theoretical and Methodological Approaches to Understanding and Treating Primary Chronic, Non-disease Related, Pain Conditions.

2.1 Chapter overview

In order to advance the development of a working theoretical model of MS pain, the following chapter will briefly summarise evidence for psychological approaches used to understand and treat individuals with primary, non-disease related, chronic pain conditions. First, a brief context surrounding current conceptualisations of chronic pain will be outlined, along with definitions used within this thesis. Second, a critical evaluation of empirical evidence for the most prominent theoretical models and frameworks attempting to understand and treat primary chronic pain conditions will be discussed. The chapter will then conclude with a brief summary of how these approaches may be relevant to MS pain. The evolution of research developing psychological theories in chronic pain is voluminous extending over half a century. Therefore, the author will selectively summarise this literature, acknowledging this chapter does not reflect an exhaustive account due to the limited scope of this thesis.

2.1.1 Defining primary chronic pain

According to the International Association of the Study of Pain (IASP) (Merskey, 1986), the need for a universal taxonomy of painful conditions was first highlighted by John Bonica in the late 1970s (Bonica, 1979). This resulted in a classification of chronic pain issued by the IASP Taxonomy Working Group in 1986, defining pain as:

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey, 1986, p.226).

Bonica had also previously defined chronic pain as pain which persists past the normal time of healing (Bonica, 1954). In practice this may be less than one month, or more often, more than six months (Merskey, 1986). For the sake of clarity and simplicity, the proceeding chapters of this thesis will refer to *primary chronic pain conditions* or

primary pain where pain is presented as the primary complaint. This is in contrast to pain which is specified in relation, or secondary, to a long-term condition (e.g. MS).

2.2 Conceptualising chronic pain

2.2.1 Evolution of a biopsychosocial perspective in chronic pain

One of the earliest explanations of pain was proposed by the French philosopher Rene Descartes (Descartes, 1989), who described pain mechanistically, in dualistic mind and body terms, and suggested that tissue damage was a necessary condition for pain to occur. The prevailing Cartesian view meant that conceptualisations of pain remained mostly physiological throughout the early part of the 20th century (Gatchel, Peng, Peters, Fuchs, & Turk, 2007). However, the advent of psychoanalytic perspectives saw the rise of psychosomatic explanations of pain, which dichotomised painful symptoms as either physiological or psychological in nature, where inexplicable remitting and relapsing conditions, such as rheumatoid arthritis, were categorised as psychiatric 'hysterical conversion disorders' (Alexander, 1950). The dichotomised view that pain either existed in the mind or body was later reflected in research investigating predisposing pain personality types of people with medically unexplained pain. This included the now widely refuted 'Conversion V' and 'Neurotic Triad' pain personality profiles, derived from the Minnesota Multiphasic Personality Inventory (MMPI) (Eccleston, 2011; Pilling, Brannick, & Swenson, 1967), which grew in popularity during the 1960s. 'Conversion V' depicted a V-shape pattern from composite scores on the MMPI, which identified individuals who experienced somatic symptoms in response to stress, expressed exaggerated concern over bodily sensations, and were unable to recognise their own emotional state. The 'Neurotic Triad' reflected a similar pattern, except these individuals were described as more demanding and complaining (Leo, 2007).

Around this time a shift towards a more integrated biopsychosocial understanding of pain physiology led to the introduction of gate control theory, proposed by Ronald Melzack and Patrick Wall (Melzack & Wall, 1967), and later Kenneth Casey (Melzack & Casey, 1968). Gate control theory provided a more complex, integrated multidimensional explanation of pain, which drew on both psychological findings (Beecher, 1959; Pavlov, Gantt, Volborth, & Cannon, 1941) and a combination of

specificity and pattern theories derived from clinical assessments (Hebb & Konzett, 1949; Livingston, 1943). Together this evidence did not support a one-to-one relationship between pain perception and pain intensity of a stimulus, or that observable tissue damage was a pre-requisite for pain to occur. In addition, the traditional view that "pain receptors" function only by sending afferent messages to the brain was challenged. Rather gate control theory proposed that ascending signals related to pain and injury could be intensified, reduced or blocked by other incoming stimuli via modulatory control systems located within the brain and body before reaching the perceptual centres of the brain. The gating mechanisms were hypothesised to 'open' and 'close' according to feedback from nerves in the body, including descending impulses from the brain activated by specific neural signatures or networks (including e.g. attention, emotion or memory processes). Therefore, in conjunction with Melzack and Wall's later neuromatrix theory (Melzack & Wall, 1996), gate control theory acknowledged the important role genes, psychological factors or processes, and the environment play in the experience of pain. Whilst gate control theory was not explicitly described as a "biopsychosocial model", it was consistent with the later work of George Engel (Engel, 1977), who was one of the first to propose that a biomedical reductionist philosophy limited understanding of all health problems. Engel proposed that a broader biopsychosocial perspective was needed to fully account for determinants of health and disease, highlighting that chronic physical illness had previously been conceptualised only in terms of underlying physical mechanisms to the exclusion of behavioural or psychosocial elements.

Engel's work and gate control theory provided an important foundation for the development of a biopsychosocial model of pain, which viewed chronic pain as a dynamic and reciprocal interaction between biological, psychological, social and cultural variables that ultimately shapes a person's response to pain (Turk & Okifuji, 2002). What followed was an evolution of predominant psychological paradigms (now described in terms of 'waves') aiming to understand and treat chronic pain, and the development of specific therapies. At present there is no single unifying model of chronic pain, but several have reasonable empirical support. There are also several other specific therapeutic approaches that have been applied to chronic pain, including mindfulness, hypnosis, biofeedback and motivational interviewing (Jensen et al., 2009; Jensen, Ehde, et al., 2011; Jensen et al., 2003; Kabat-Zinn, 1982; Kabat-Zinn, Lipworth, & Burney, 1985; Kaushik, Kaushik, Mahajan, & Rajesh, 2005; Nestoriuc & Martin,

2007; Nestoriuc, Martin, Rief, & Andrasik, 2008). However, these are based on, in some cases, a broader understanding of psychological phenomena, and are not specific to chronic pain. Therefore, this review will only examine the predominant approaches that have developed specific theories of chronic pain, which have directly informed the development of specific treatments.

2.3 Models and frameworks for understanding chronic pain

2.3.1 "First wave" operant behavioural approaches to chronic pain

Wilbert Fordyce (Fordyce, 1976; Main et al., 2014) was the first to develop a "first wave" operant behavioural rationale and treatment for chronic pain (Morley, 2011). According to Fordyce, this approach was influenced by Burrhus Frederic Skinner's earlier operant (Skinner, 1963) and Albert Bandura's social learning theories (Bandura, 1965). Fordyce's approach did not dismiss disease or 'psychogenic' models of chronic pain, but was the first to emphasise the importance of integrating the role of pain behaviours within a multidisciplinary treatment context. A central concept of the operant approach is "pain-behaviour". Fordyce defined pain behaviours as both verbal and paraverbal (e.g. altering the tone of voice) and nonverbal emissions (e.g. guarding, moaning, gasping, limping, rubbing painful areas, grimacing and avoidance of work-related activities etc.) In Fordyce's treatment both types of pain behaviour were conceived as emissions that, when observed by others, resulted in the observer responding contingently, so that over time behaviours become operantly controlled (Williams & Daniel, 2012). Specifically, a person's pain behaviours were argued to contribute to a three part contingency referred to as Antecedents, Behaviours and Consequences (ABCs), where the individual encounters (A) a situation or discriminative stimulus, e.g. a painful sensation (B) responds to the antecedent, e.g. pain behaviours, which may (C) interact with a variety of consequences in the social environment, e.g. others attempts to relieve the individual of responsibility for even basic activities of daily living (Kerns, Sellinger, & Goodin, 2011). The theory suggests that over time future patterns of behaviour are learned and reinforced, and directly shaped and maintained by the social and cultural context, ultimately resulting in behavioural deactivation and greater levels of distress.

Operant treatment focuses primarily on extinguishing pain behaviours, and positively reinforcing healthy, adaptive behaviours, such as exercise or work (Henschke et al., 2010). Within treatment 'healthy behaviours' are increased systemically during each session by generating an exercise schedule with a specific goal in mind. Incremental gains in performance are then maintained and reinforced by regular positive feedback and verbal encouragement from both treatment staff, spouse or family members (Fordyce, 1976; Main et al., 2014). Taken together recent meta-analytic reviews suggest that operant therapy is more effective than wait list controls and usual care for short-term pain relief, and improving mood in some cases (Henschke et al., 2010; Williams, Eccleston, & Morley, 2013). However, available evidence does not show that operant therapy is effective in the intermediate or long-term, or that it significantly improves functional status. In addition, it certainly does not appear superior in effects on pain or depressive symptoms compared to cognitive and combined behavioural therapies, and when compared to group exercise treatments over the long-term. However, one potentially important criticism of these findings is the lack of large and methodologically robust studies evaluating operant behavioural therapy in its purest form (Molton, Graham, Stoelb, & Jensen, 2007).

Fordyce's operant approach to chronic pain has been subject to several criticisms. First, researchers suggest the operant approach oversimplifies the role of social contingencies on behaviour (Williams & Daniel, 2012). Second, the strength of evidence supporting the underlying theory and terms has been described as a limited, highlighting in particular the questionable validity and narrow focus of the 'pain behaviour' construct (McCracken, 2014; Turk, 1996). Third, Fordyce's approach tended to understate the role of cognition and other psychological processes that may contribute to pain and related disability. However, it has been suggested that Fordyce's shared conceptualisations, or formulations, with patients means that operant treatment is inherently cognitive and behavioural in nature (Sharp, 2001). Finally, although Fordyce's approach claims roots in operant theory, some have argued it is insensitive to social and cultural norms, and underestimates the extent to which a person's ability to adapt behaviourally is contextually determined (Williams & Daniel, 2012).

2.3.2 "Second wave" traditional cognitive behavioural approaches to chronic pain

Around the same time as Fordyce's earlier work (Fordyce, Fowler, Lehmann, & Delateur, 1968), the prevailing view within the wider field of psychiatry and psychology was that behavioural approaches generally reflected a purely deterministic perspective that de-emphasised individual autonomy (Williams & Daniel, 2012). Operant and other behavioural approaches were also criticised for being unable to clearly articulate a fully integrated account of human cognition (Chomsky, 1959; O'Donohue, 1998), which resulted in the widely held view that behavioural principles required expansion.[3] This led to second-generation behaviour therapy, and a subsequent paradigm shift to what was at one time called the "cognitive revolution", which included Cognitive Therapy (CT) pioneered by Aaron Beck and colleagues (Beck, 1976; Beck, 1979), and Rational-Emotive Therapy (RET) by Albert Ellis (Ellis, 1980; Ellis & Bernard, 1985). The purpose of these approaches was to provide a therapy that could explain and treat cognition for people experiencing depression, which unlike its psychoanalytic predecessor, could be tested empirically, and was based on testable empirical models (Beck, 1979). "Second-wave" approaches incorporated the earlier principles of conditioning, and used a computational metaphor to conceptualise cognitive mechanisms (Dougher & Hayes, 2000; O'Donohue, 1998).

The *cognitive behavioural perspective*, a term comprising a diversity of integrated approaches (Mahoney & Arnkoff, 1978), was initially applied to chronic pain through the work of Dennis Turk and colleagues in the early 1980s (Turk et al., 1983), and is still applied in contemporary clinical settings today. Rooted in stoicism (Beck, 1976), the cognitive behavioural perspective suggests people have the belief they cannot function because of pain and are helpless to improve their circumstances (Turk, Swanson, & Tunks, 2008). CBT proponents were opposed to what they saw as more deterministic behavioural perspectives, and instead argued that people are not passive

[3]Noam Chomsky is recognised for his critique of B.F. Skinner's earlier operant account of cognition, or verbally regulated behaviour, which was purely theoretical in nature and attempted to explain rule-governed or instruction behaviour (Skinner, 1957). However, in more recent years a resurgence of interest in the behavioural analytic tradition has resulted in a more comprehensive operant view of language and cognition called Relational Frame Theory (RFT) (see section 2.3.3 and (Hayes, Barnes-Holmes, & Roche, 2001)), which has attempted to address gaps identified in Skinner's earlier theory.

reactors, but rather active processors of information (Turk et al., 2008). Based on this information processing model, an individual's learning history is assumed to organise a "cognitive schema" (or mental structure) representing perceptions of the self, world or future (Beck, 1991). When the individual encounters novel or familiar situations schema may be activated resulting in appraisals, expectancies or beliefs. Cognitions are hypothesised to influence mood, affect, physiological responses, and behaviour, which impact on consequences experienced, including social consequences. Each of these factors influence the nature and content of a person's thought processes, such that behaviour is reciprocally determined by both the individual and social environment (Turk et al., 2008).

Similar to Beck's Cognitive Therapy (Beck, 1976), the *cognitive behaviour therapy approach* (CBT) in chronic pain is defined as a collaborative psychotherapy, aiming to help individuals identify, reality-test and correct maladaptive, or distorted, conceptualisations and dysfunctional beliefs about pain and associated distress (Turk et al., 1983). Individuals are encouraged to learn a new psychological framework and set of terms to re-conceptualise their problem. This involves observing links between cognition, affect, physiological autonomic arousal and behaviour, including adaptive and maladaptive coping strategies, and their combined consequences (Sharp, 2001), or potential to maintain psychological and physical problems. A key focus of CBT is to help individuals identify and self-monitor the influence of negative automatic thoughts and mental images that maintain maladaptive behaviour, and using cognitive-restructuring techniques, replace them with more adaptive or beneficial ones (Turk et al., 1983). The person is encouraged to test the effects of cognitions and beliefs through tailored homework assignments forming part of a goal-oriented, systematic procedure (Kerns et al., 2011). Contemporary CBT also combines education and skills training related to stress management, including relaxation and distraction techniques, but also goal-setting, graded exposure to activity and exercise, pleasant activity scheduling, pacing of activities, assertiveness training and problem-solving (Kerns et al., 2011; Turk et al., 2008). Individuals are encouraged to reinforce and generalise newly acquired skills to a broader range of everyday life situations, and anticipate relapse by considering how they might cope with pain and distress when problems recur (Turk et al., 1983).

Whilst there are many potentially modifiable psychological constructs or mechanisms within the cognitive behavioural perspective and approach (Jensen, 2011; McCracken & Morley, 2014), two of the most studied include pain-related self-efficacy and pain catastrophizing. Pain-related self-efficacy relates to the central focus being on problems, which are viewed as specific and solvable, rather than vague, undifferentiated and overwhelming (Turk et al., 2008). The overarching focus of treatment is to facilitate an individual's perception of self-control by enhancing self-efficacy (Kerns et al., 2011; Turk et al., 2008). In the context of chronic pain, Bandura's self-efficacy concept (Bandura, 1977) is defined as the person's confidence in their ability to engage in a course of action sufficient to accomplish a desired outcome, such as control of pain, and limiting its impact on one's life (Turk & Okifuji, 2002). The expectation is that individuals will gain mastery over their pain, resulting in improved mood (Thieme, Gromnica-Ihle, & Flor, 2003). Evidence suggests that pain-related self-efficacy is a strong predictor of improved outcomes in primary chronic pain populations (Keefe, Rumble, Scipio, Giordano, & Perri, 2004; Turk & Okifuji, 2002). Whilst self-efficacy has been identified as an important factor in chronic pain, recent theoretical approaches have begun to question traditional CBT's focus on enhancing perceived control and emphasis on problem-solving, suggesting that attempts to do so may inadvertently result in poorer outcomes (Eccleston & Crombez, 2007; McCracken, 2007; Vowles, McNeil, et al., 2007).

Another potentially modifiable psychological construct within traditional CBT for chronic pain is pain catastrophizing, defined as an exaggerated negative orientation towards pain where a relatively neutral event is irrationally made into a catastrophe (Sullivan, Bishop, & Pivik, 1995). Pain catastrophizing has three dimensions, comprising magnification, rumination and helplessness. Consistent with pain-related self-efficacy, pain catastrophizing has also been defined as the tendency to focus on pain and negatively evaluate one's ability to deal with it (Keefe et al., 2004). However, some researchers suggest there are grounds for proposing a general rather than pain-specific view of catastrophizing (Sullivan, 2001). Three reviews suggests that pain catastrophizing is one of the most robust predictors of pain outcomes and behaviours in clinical and experimental studies, but the majority have been cross-sectional in design, limiting causal interpretation (Edwards, Bingham, Bathon, & Haythornthwaite, 2006; Quartana, Campbell, & Edwards, 2009; Sullivan, 2001). However, a growing number of studies indicate that pain catastrophizing, along with perceived control in some cases, is

an important mediator of pain severity, pain interference, depression and pain behaviour in CBT trials, along with other treatments, for chronic pain (Burns, Day, & Thorn, 2012; Smeets, Vlaeyen, Kester, & Knottnerus, 2006; Spinhoven et al., 2004; Turner J.A., Holtzman S., & Mancl L., 2007). However, one criticism is that research on pain catastrophizing has mostly been empirical and not based on a systematic theory (Keefe et al., 2004). Whilst catastrophizing features in both the traditional CBT and fear-avoidance models of chronic pain (outlined in section 2.3.2.1), it has been variably defined as both an appraisal, attentional and coping-related construct (Sullivan, 2001). For example, some researchers have conceptualised pain catastrophizing as a coping response designed to deal with negative emotions caused by chronic pain by eliciting proximity to, or garnering support from, others (Sullivan, 2001). In addition, others have argued that pain catastrophizing may reflect a measure of distress, or a component of distress (Turner & Aaron, 2001). Consequently, pain catastrophizing has been criticised for being a theoretically multifactorial construct (Severeijns, Vlaeyen, & van den Hout, 2004). Despite these limitations, both pain-related self-efficacy and pain catastrophizing remain common targets in contemporary CBT treatments.

There is now a large body of evidence suggesting interventions defined as CBT can improve function as well as reduce pain severity, pain interference and pain behaviours (Turk et al., 2008). Consistent with several other reviews in the field (Bernardy, Füber, Köllner, & Häuser, 2010; Dixon, Keefe, Scipio, Perri, & Abernethy, 2007; Henschke et al., 2010; Hoffman, Papas, Chatkoff, & Kerns, 2007; Scascighini, Toma, Dober-Spielmann, & Sprott, 2008), a recently updated Cochrane review of 35 RCTs evaluating CBT for chronic pain (Williams et al., 2013) show moderate effects on improved mood, and small effects on catastrophic thinking, disability and pain severity. The review also found superior effects for CBT compared to variants of operant behaviour therapy. However, the review authors concede that many of the so-called "CBT" interventions evaluated showed significant sample and treatment heterogeneity, which limits more definitive interpretation of the overall effects of the CBT approach for chronic pain.

Several limitations of CBT are highlighted in the chronic pain literature. First, review findings in chronic pain are limited by considerable variation in the content of interdisciplinary pain management programmes utilising CBT, making it is difficult to determine which therapeutic components best predict improvement (Kerns et al., 2011; McCracken, Vowles, & Eccleston, 2005; Williams et al., 2013). Second, researchers

highlight a lack of coherent theory underlying many intervention studies (Williams et al., 2013). At the conceptual level, some have argued there is a lack of organisation for the numerous dimensions or mechanisms proposed within CBT models, and that scientific assumptions have yet to be stated, but are likely to be varied (McCracken & Morley, 2014). Finally, treatment reviews consistently demonstrate that although CBT is helpful for many individuals, there are some for whom CBT is not beneficial (Turk et al., 2008; Williams et al., 2013). For example, one practice-based evaluation of an interdisciplinary chronic pain management programme based on CBT shows that between 1 in 3, and 1 in 7 (depending on the outcome measure used), achieve clinically significant gains at post-treatment and follow-up, whilst around 1% to 2% of patients deteriorate during treatment (Morley, 2008).

2.3.2.1 Fear-avoidance model of chronic pain

Within the broader category of traditional CBT more specific psychological theories of chronic pain have developed in recent years. One is the fear-avoidance (FA) model of chronic pain (Lethem, Slade, Troup, & Bentley, 1983; Vlaeyen & Linton, 2000), which suggests that a person may interpret potentially pain-inducing situations as threatening and as causing further harm or damage to the body (Boersma & Linton, 2006; Gatchel et al., 2007). Within this model pain-related anxiety, fear and catastrophizing are thought to accentuate pain experience (Crombez, Eccleston, Van Damme, Vlaeyen, & Karoly, 2012; Crombez, Vlaeyen, Heuts, & Lysens, 1999), contributing to a cycle of hypervigilance, behavioural avoidance and inactivity, resulting in greater pain severity and pain interference (see Figure 3). Consistent with pain catastrophizing, pain-related anxiety or fear-avoidance have also been identified as significant predictors of greater pain-related disability in chronic pain populations (Keefe et al., 2004; Turk & Okifuji, 2002). However, one review suggests that studies testing the FA model within longitudinal designs using path-analytic methods has yielded conflicting or null findings (Asmundson, Parkerson, Petter, & Noel, 2012).

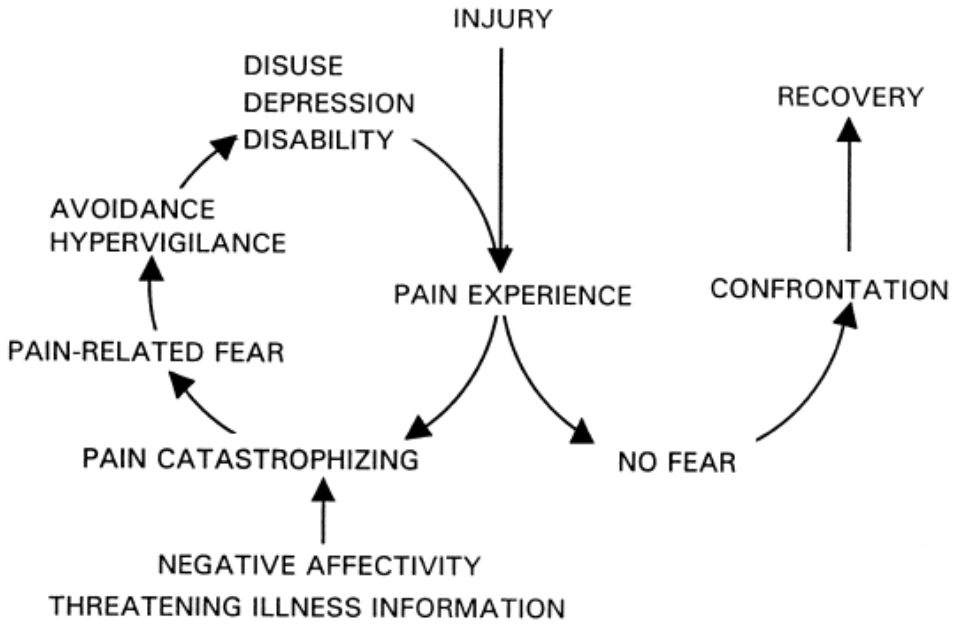

Figure 3: Fear-Avoidance of Chronic Pain (Vlaeyen & Linton, 2000)

A key strength of the FA model is that it maps directly onto graded *in vivo* exposure and graded activity treatment techniques. These aim to help individuals engage in physical activities for the purpose of reducing fear associated with the particular activity (Keefe et al., 2004). The evidence-base for graded *in vivo* exposure is growing, and a recent review indicates that it is superior to no treatment at all in the short to intermediate term, and is comparable to physical exercise interventions (Macedo, Smeets, Maher, Latimer, & McAuley, 2010). Another review (Bailey, Carleton, Vlaeyen, & Asmundson, 2010) also suggests that graded *in vivo* exposure demonstrates comparable efficacy to "third-wave" approaches, such as Acceptance and Commitment Therapy (ACT) (see section 2.3.3), and may be more effective in improving disability and reducing fear of pain and pain severity compared to wait-list controls, graded activity and mixed protocols of CBT. A limitation of this review is that there was considerable inconsistency in study protocols and outcomes, which precluded meta-analysis and more definitive conclusions regarding efficacy.

Several limitations of the FA model and graded *in vivo* exposure techniques have been identified. First, it has been suggested that the FA model and graded *in vivo* exposure techniques address only one narrow pathway leading to disability, which does not take into account other contextual influences (Keefe et al., 2004; McCracken & Morley, 2014). Other researchers have argued that addressing fear in a cognitive framework

needs to be delivered in conjunction with improving the person's conceptual understanding of pain (Williams & Daniel, 2012). It is assumed this understanding provides a context to help individuals re-evaluate unhelpful beliefs and fears about pain's causes or triggers, and understand the meaning of fluctuating pain.

2.3.2.2 Avoidance-endurance model of chronic pain

A more recent extension of the FA model of chronic pain has also been proposed. In addition to the FA response, the avoidance-endurance (AE) model of chronic pain incorporates two alternative pathways hypothesised to result in greater disability (Hasenbring, Hallner, & Rusu, 2009; Hasenbring & Verbunt, 2010). First, the distress-endurance (DER) response is characterised by attempts to suppress pain, which may increase anxiety or depression, followed by an increase in task persistence behaviour, ultimately leading to physical overuse and overload, chronic pain and reduced functioning (see Figure 4). Second, the eustress–endurance response (EER) suggests that some individuals use focused distraction, which can result in positive mood in the short-term despite pain, followed by task persistence. These individuals are thought to recover from pain in the short-term, but develop chronic problems in the long-term (Hasenbring, Chehadi, Titze, & Kreddig, 2014). The model also suggests that a more adaptive responder will oscillate flexibly between these avoidant behavioural responses in different situations.

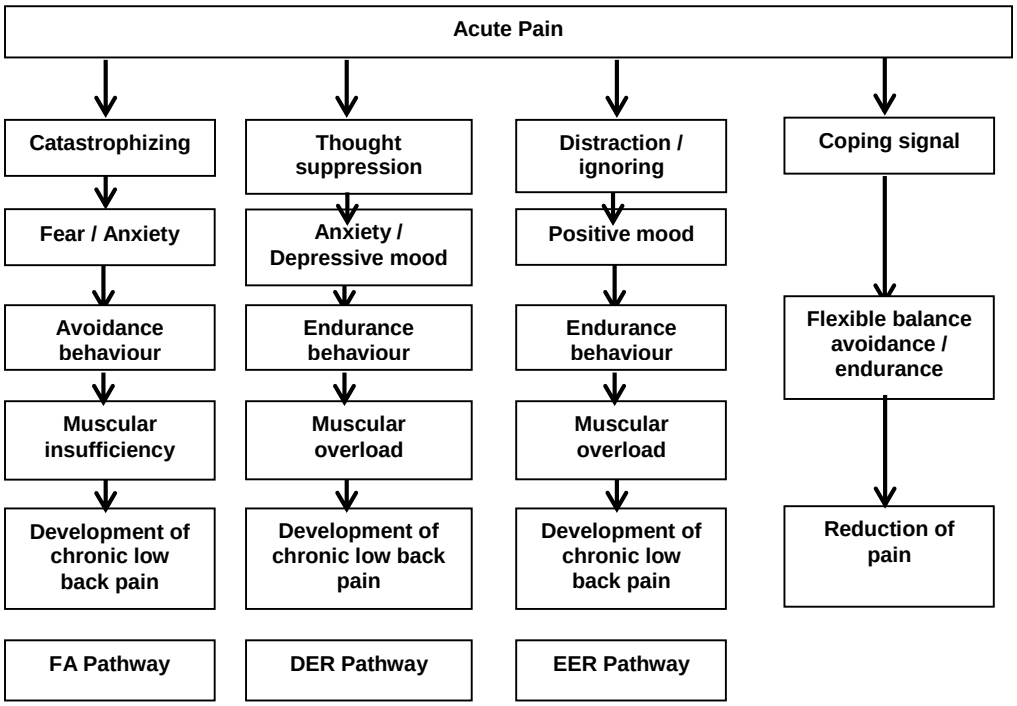

Figure 4: Avoidance-Endurance Model of Chronic Pain (Hasenbring et al., 2014)

To date the FA element of the AE model has received significant research attention, although there are currently only a limited number of studies investigating the DER and EER pathways. Studies examining these elements have tended use longitudinal designs (Hasenbring et al., 2014) and, consistent with qualitative accounts of people with chronic pain (Andrews, Strong, Meredith, Gordon, & Bagraith, 2015), offer preliminary evidence for both types of responding. One experimental study has shown that greater fear-avoidance responding is associated with increased cortisol levels in healthy adults during a cold-pressor procedure, whilst endurance responding was not (Sudhaus et al., 2015). As hypothesised by AE model, this suggests endurance responding may be a positive way of coping with pain at least in the short-term. However, results from healthy individuals subjected to transient pain exposures within lab-based studies may not always generalise to chronic pain populations. One intervention study has shown that two versions of CBT, one specifically targeting pain-related avoidance (n = 93), and the other persistence responses using activity pacing techniques (n = 97), resulted in improvements in physical and psychological functioning in both treatment groups compared to controls (Van Koulil et al., 2011). Effects on psychological functioning in each treatment group were mediated by hypothesised changes in either pain avoidance or persistence responding. However, only the effects observed in physical functioning outcomes in the activity pacing group were mediated by pain-persistence responses.

One limitation was that both treatments also showed significant improvements in other relevant cognitive behavioural factors or processes (e.g. pain-related fear, hypervigilance, worry, acceptance and helplessness), which were not tested for mediation alongside avoidance and endurance variables. Therefore, it remains unclear which factors or processes reflect the most important targets in CBT.

The AE model also has limitations. Whilst it offers two alternative explanations of pain-related disability, expanding the narrower focus of the FA model, it has been argued that elements in both pathways reflect more specific topographical, or "surface level", descriptions of potentially unhelpful cognitions, emotions and behaviours, and fail to clearly take into account the functional dimension of behaviour (McCracken & Morley, 2014). Consistent with Hasenbring's argument that healthy functioning may reflect a flexible movement between these avoidance responses (Hasenbring et al., 2014), it might be that an individual's avoidance or persistence behaviour may actually reflect an 'adaptive' response to pain in certain circumstances. Therefore, a broader class of experiential avoidance behavioural processes may better account for the function, rather than description, of a person's behaviour in a given context. Another related criticism of both the AE and FA models is that they do not adequately explain the potentially important role of motivational or recovery processes in chronic pain (McCracken & Morley, 2014).

2.3.2.3 Common sense model of illness perceptions applied to chronic pain

The cognitive models of chronic pain have also led to an interrelated body of research looking at pain-related beliefs more broadly, which have also been shown to be associated with key outcomes. Some of these studies have been less guided by a clear theory of chronic pain (Jensen, Karoly, & Huger, 1987; Jensen, Romano, Turner, Good, & Wald, 1999; Jensen, Turner, Romano, & Lawler, 1994; Turner, Jensen, & Romano, 2000). In contrast, others have been informed by broader psychological theories that are less specific to pain (Foster et al., 2008; Foster, Thomas, Bishop, Dunn, & Main, 2010; Moss-Morris, Humphrey, Johnson, & Petrie, 2007), drawing on the common sense model of illness perceptions (CSM) proposed by Howard Leventhal and colleagues in the 1980s (Leventhal, Nerenz, & Steele, 1984).

Briefly, the CSM is a cognitive behavioural model based on self-regulation, which explains how individuals interpret, process and manage potential health threats related to prevention, adaption and maintenance of behaviours relating to disease (Leventhal, Meyer, & Nerenz, 1980; Leventhal et al., 1984). As shown in Figure 5 the CSM suggests two parallel, and partly interacting, systems, which are activated in response to health threats (i.e. symptoms and other internal or external cues). First, the cognitive processing pathway is responsible for generating illness representations, or schema, including thoughts related to (a) symptoms attributed to the chronic condition (identity), (b) duration of illness (timeline), (c) potential causes (cause), (d) illness severity and its potential impact on physical, social and psychological functioning (consequences), (e) the extent to which the person believes their illness is curable or controllable, relating to efficacy of personal and treatment resources for managing the health threat, and (f) overall understanding of illness (illness coherence). Illness representations are thought to drive coping strategies or management behaviours to deal with the health threat, which in turn are evaluated for their effectiveness. Depending on the nature of this "secondary appraisal", the individual may continue with a specific coping strategy or adopt an alternative. With new information, illness perceptions are thought to be constantly updating and coping behaviours continuously appraised for their efficacy. The emotional processing system (emotional representation) is also thought to be activated by illness representations and other internal (e.g. physical sensations) and environmental cues. Once activated this can also result in the implementation of potentially helpful or unhelpful self-management behaviours or coping strategies (e.g. avoidance, expression or suppression of feelings), which ultimately aim to reduce or control negative emotions.

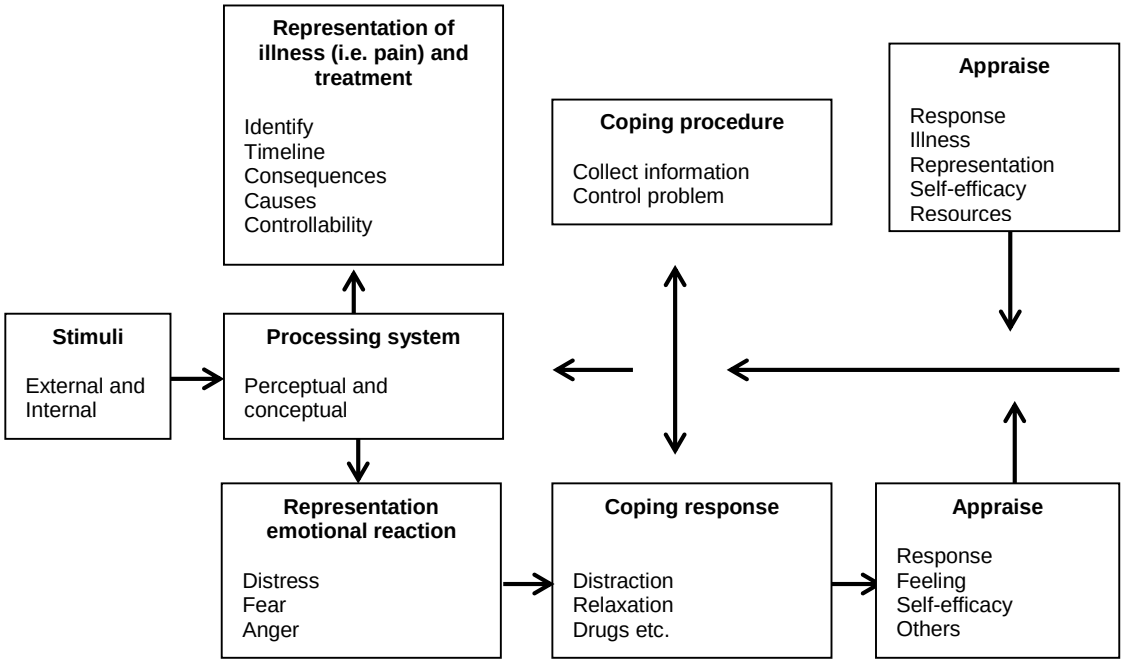

Figure 5: Common Sense Model of Illness Perceptions (Leventhal et al., 2003)

Whilst the CSM is not a dominant theory in chronic pain, a growing body of longitudinal evidence indicates that individual's perceptions related to the consequences, chronicity (timeline acute/chronic), personal (and treatment) control of chronic low back pain at baseline predicts outcome at six months follow-up (Foster et al., 2008). Specifically, individuals who perceived low back pain as chronic, uncontrollable and as having serious consequences were more likely to have poorer outcomes at 6 months. Another study in primary care has also shown that chronic pain patient's perceptions of illness identify, acute/chronic timeline, personal control, and pain self-efficacy at baseline explained a large proportion (56%) of the variance in outcomes at 6 months (Foster et al., 2010). Importantly, these illness representations remained significant in an adjusted multivariate analysis, whilst other traditional CBT factors, including depression, catastrophizing and fear avoidance did not. This suggests that whilst psychological constructs share some conceptual overlap, more general CBT constructs may be less important when set against pain perceptions specific to the CSM. These findings were mostly consistent with a longitudinal study exploring changes in cognitive variables across a four week multidisciplinary group pain management program based on reactivation, which included components of CBT (Moss-Morris et al., 2007). Findings indicated significant reductions in perceived consequences and catastrophizing were most strongly associated with improved physical functioning, whilst reduced pain vigilance and negative emotional representations, and increased

coherence of pain, were the best predictors of improved mental functioning. Taken together these findings offer promising support for the idea that pain perceptions from the CSM are likely to be important targets within CBT treatments for chronic pain. However, these factors have yet to be examined in mediation analyses within the context of RCTs specifically evaluating CBT treatments for chronic pain.

2.3.3 "Third wave" contextual cognitive behavioural approaches to chronic pain

Chronic pain was one of the first problems addressed by so-called "third-wave" approaches, including Mindfulness-Based Stress Reduction (MBSR), pioneered by Jon Kabat-Zinn in the early 1980s (Kabat-Zinn, 1982, 1994). However, some have argued there has been little robust evaluation of MBSR in chronic pain since this time (for recent reviews see Chiesa & Serretti, 2011; Teixeira, 2008), and even fewer theoretical developments informing key mechanisms of action, despite becoming increasingly widespread in clinical environments (Williams & Daniel, 2012). In contrast, a newer form of CBT, called Contextual Cognitive Behavioural Therapy (CCBT) (McCracken, 2006), synonymous with ACT (Hayes, 1999), has received increasing research attention in the context of chronic pain since the late 1990s (McCracken, 1998). ACT first appeared in the wider field of clinical psychology in the early 1990s for mood disorders (Zettle, 2005), and was informed by a basic scientific account and research programme that began around a decade before this time, leading to the development of relational frame theory (RFT). Briefly, RFT is a post-Skinnerian operant account of human language and cognition (Hayes et al., 2001), centring around notions of experiential avoidance, generalised response classes and "relational responding" (McCracken, 2014) (see Torneke, 2010 for a more comprehensive summary). RFT and ACT are founded on the philosophical assumptions of functional contextualism, which applies a pragmatic truth criterion to scientific enquiry (Hayes et al, 2006). Contextualism is defined as a world view, or hypothesis, with an underlying root metaphor of the "act in its context", whereby any event is interpreted as an ongoing act inseparable from its current and historical context (Pepper, 1942). This means all actions are viewed as whole events, which have meaning only with reference to their context. The truth criterion of contextualism is therefore defined as a "successful working" toward one's analytic goals, whereby the truth and meaning of a concept lies in its function or utility, rather than in how well it is said to describe, represent, or mirror reality (Hayes, 1993). Consistent with philosophical pragmatism (James, 1909), a contextual analysis can be

said to true or valid if it leads to effective action, or achieves some pre-specified goal. Together RFT and ACT aim to provide a functional contextual account of human behaviour that focuses on the prediction and influence of psychological events, with precision, scope, and depth, within the behaviour of the person interacting in and with a context considered historically and situationally (Hayes, Levin, Plumb-Vilardaga, Villatte, & Pistorello, 2013) (for a recent summary of the philosophical assumptions of RFT and ACT see Vilardaga, Hayes, & Schelin, 2007). Specifically, from a functional contextual perspective, an interpretation of human behaviour is said to have precision, scope and depth when it possesses the following qualities: (1) identifies variables that permit prediction (of the events in question) and influence (i.e. can be manipulated to affect the probability of an event occurring), (2) has a limited number of concepts (i.e. specific in how it applies), (3) but is broad in situations to which it is relevant (e.g. across health problems or diagnostic groups), (4) coheres with different levels of analysis (e.g. experimental or applied science) and other branches of science, and (5) has the built-in feature of being ‘‘constantly updating’’, which means the philosophy is held consistently out of choice, but the model and treatment methods that emerge from it are held lightly, with the expectation that they will, at some stage, be shown to be limited in some way (McCracken & Morley, 2014).

ACT’s applied or “mid-level” psychological flexibility model has been described as a transdiagnostic theory of “normal” human behaviour, which incorporates functional dimensions of analysis and “motivational” processes (McCracken & Morley, 2014). “Mid-level” refers to the applied constructs, or processes, in the psychological flexibility model, which are in themselves derived from the more complex, or finer grained, basic level behavioural processes operationalized in RFT. Psychological flexibility has been defined as the capacity to persist with, or change, behavior in a manner that includes conscious and open contact with thoughts and feelings, appreciates what the situation affords, and serves one’s goals and values (Scott & McCracken, 2015). The psychological flexibility model comprises six integrated psychological processes (see Figure 6 below), including acceptance, cognitive defusion, self-as-observer, present-moment awareness, values, and committed action (Hayes, 1999). The six processes are more extensively described in other sources (Hayes, Luoma, Bond, Masuda, & Lillis, 2006; Hayes, 1999). Briefly, acceptance is defined as willing engagement in activities in a way that includes contact with one’s unwanted experiences, such as pain, without defense or attempts to struggle with or control them,

when to do this serves one's goals (McCracken, 2010a; McCracken & Morley, 2014; McCracken, 2010b). Cognitive defusion is the ability to experience a distinction between thoughts and the things they describe, and to contact experiences directly without being dominated by the meaning and influences carried in thoughts (McCracken & Morley, 2014). Self-as-observer is closely linked to RFT's deictic relational frames, including *I* versus *You*, *Now* versus *Then*, and *Here* versus *There*, which lead to a sense of self as a locus or perspective (Hayes et al., 2006; McHugh, 2015). It therefore reflects the person's ability to experience a perspective where they are neither defined, nor harmed, by their own thoughts and feelings (McCracken & Morley, 2014). Present-moment awareness, or flexible present-focused attention, is similar to the qualities cultivated in mindfulness meditation. Unlike goals, values are freely chosen qualities of purposive action that we define as important, which are ongoing and can never be obtained as an object, but can be instantiated moment by moment (Hayes et al., 2006) and can feed into goals (McCracken & Morley, 2014). Finally, committed action is the ability to flexibly persist with a course of action guided by values and goals, in a way that can incorporate failure and discomfort, and still continue, but also be abandoned when unhelpful (McCracken, 2013; McCracken & Morley, 2014). The inverse of the six psychological flexibility processes represents a model of behavioural problems and suffering, including experiential avoidance, cognitive fusion, an inability to take a perspective separate from thoughts and feelings, a pre-occupation with the past or future, failures in clarity or pursuit of values, and inflexible persistence or impulsive avoidance (McCracken & Morley, 2014).

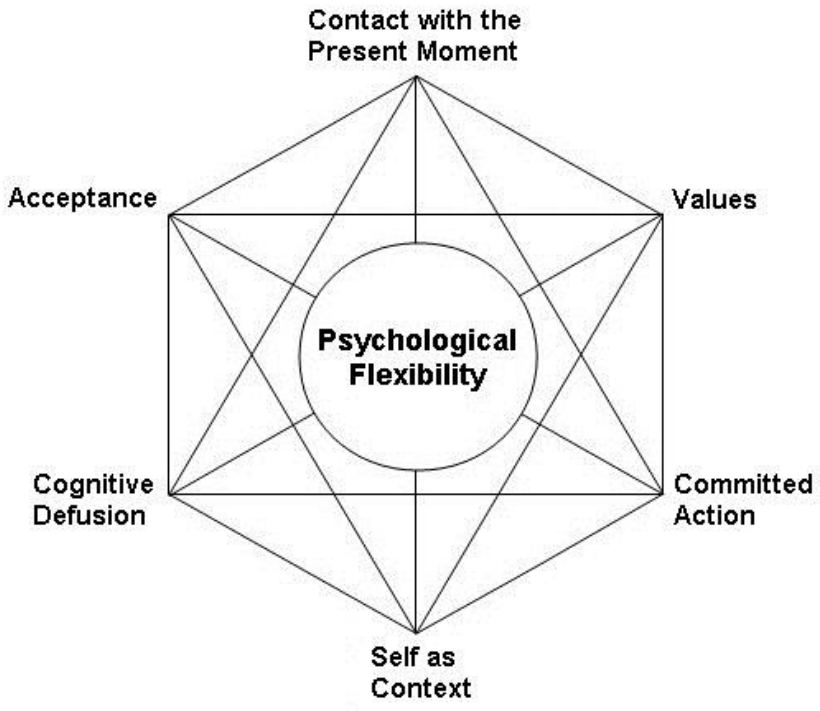

Figure 6: ACT's Psychological Flexibility Model (Thompson & McCracken, 2011)

A recent review of 66 studies shows there is now a range of laboratory-based component research supporting most elements of the psychological flexibility model (Levin, Hildebrandt, Lillis, & Hayes, 2012), including many studies examining brief pain exposures. In contrast, much of the applied research on the psychological flexibility model in chronic pain has focused on the role of pain acceptance and values (see Scott & McCracken, 2015 for a recent review). Whilst many studies are cross-sectional in nature (Reneman, Dijkstra, Geertzen, & Dijkstra, 2010), limiting causal interpretation, there is also a growing number of process-level studies using mostly non-randomised longitudinal treatment designs (Scott & McCracken, 2015). Overall, these show that psychological flexibility processes are consistently associated with pain severity, pain interference and other relevant domains of functioning. Recently there have also been efforts to operationalise other processes within the psychological flexibility model, which have demonstrated significant predictive relationships between pain outcomes and "decentering", a similar construct to cognitive defusion (McCracken, Gutiérrez-Martínez, & Smyth, 2012), as well as present moment awareness (McCracken, Gauntlett-Gilbert, & Vowles, 2007), and committed action (McCracken, 2013).

Proponents of ACT suggest it is not a theory or scientific model per se (McCracken & Morley, 2014). Rather the six psychological flexibility processes map directly onto a set of mindfulness and acceptance, or commitment and behaviour change, treatment methods or techniques (Hayes et al., 2006). Alongside RFT, the psychological flexibility processes offer guidance on how to approach the therapeutic relationship to increase psychological flexibility from a pragmatic stance. Experiential exercises help clients come into contact with psychological processes more directly, and use of metaphorical language, paradoxes, and stories are introduced by the therapist to help the person learn to relate to their experience in a more flexible way without constructing a new set of rigid rules (Hayes et al., 2013). Movement in the six processes is the functional goal and any techniques that shift these processes can form part of an ACT intervention (Hayes et al., 2013). However, ACT is not didactic in style and does not attempt to directly alter the severity of pain and pain-related emotions, such as fear and frustration, nor does it seek to alter the *content* of thoughts about pain. Rather, it aims to alter how the person relates to these experiences to improve the quality and effectiveness of action (Scott & McCracken, 2015) and reduce the distressing and disabling influences of pain on living life according to one's values (McCracken *et al.*, 2005).

Four systematic reviews have examined the efficacy of ACT in the context of chronic pain. Whilst one review has been described above (Bailey et al., 2010), a subsequent meta-analysis including 22 studies indicates that 9 RCTs for ACT and MBSR show small pooled effect sizes for pain severity, anxiety, depression, quality of life, and medium effects for depression for pre- and post-treatment changes. These findings are comparable to traditional CBT, suggesting both may be good alternatives (Veehof, Oskam, Schruers, & Bohlmeijer, 2011). Pooled effects for 13 controlled and uncontrolled trials were also in the medium range on most outcomes. One limitation of this review was that ACT and MBSR were grouped together as "acceptance-based treatments", making it difficult to disentangle their potentially divergent treatment methods. Another limitation was that only two of the seven ACT studies in the review were RCTs, since non-randomised studies are more susceptible to bias. More recently, a meta-analytic review (Öst, 2014) examining RCTs for ACT for a range of physical and mental health problems identified 10 studies for ACT in chronic pain. However, this review did not conduct a meta-analysis, but concluded that ACT was "probably efficacious" for a number of conditions. However, Öst's review was recently criticised

because it focused exclusively on pain severity as a primary outcome of treatment to the exclusion of other relevant emotional, physical and social domains of functioning. Scott and McCracken have argued that Öst's review method contradicts the aims of ACT (Scott & McCracken, 2015). Specifically, a more recent review (Hann & McCracken, 2014) suggests that ACT deviates from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidance (Dworkin et al., 2010; Dworkin et al., 2008), which reflects a group of academics, regulatory agencies, US National Institutes of Health, US Veterans Administration, consumer support and advocacy groups, and industry, who develop consensus reviews and recommendations for improving the design, execution, and interpretation of clinical trials of treatments for pain. In contrast to IMMPACT guidance, physical and social role performance reflect primary targets in ACT, and pain severity and emotional functioning are considered secondary. The review therefore identified the same 10 studies, and showed that ACT was efficacious particularly with regard to improving physical and emotional functioning. However, overall many of the reviewed studies evaluating ACT for chronic pain were small and included significant risk of bias, and most compared ACT with inactive controls. Therefore, improvements observed may in part reflect non-specific treatment effects.

The ACT model also has limitations. The psychological flexibility model emphasises the central role of understanding contextual influences on the function of a person's behaviour, with the aim of developing theory that coheres with other branches of science. However, consistent with other chronic pain models it does not clearly explain how biology interacts with these processes, or how other's behaviour (e.g. the effects of stigma, low social support or overly solicitous responses), or the wider social context, can have a potentially positive or negative impact on people with chronic pain. In addition, whilst the psychological flexibility model focusses predominantly on the role of experiential avoidance of private events, it fails to incorporate a clear explanation of emotion and emotional processing, and their underlying biological mechanisms (see Lumley et al., 2011). Although the fear-avoidance model highlights the negative consequences of pain-related fear, other existing chronic pain theories have yet to explain the potentially important role of other emotional responses (e.g. positive affect), and how positive emotions can play an important role in facilitating awareness, and guiding and or motivating more adaptive behaviour (Lumley et al., 2011).

2.3.4 Comparing predominant approaches in chronic pain

Whilst some reviews have compared effect sizes for the different treatments in chronic pain (Bailey et al., 2010; Williams et al., 2013), few individual RCTs have directly compared the more predominant approaches. Only one study has directly compared group CBT with ACT (Wetherell et al., 2011), and another ACT with applied relaxation training (Thorsell et al., 2011). Findings indicate that support for the superiority of one or the other treatment remains unclear at present, although when ACT was compared to CBT (Wetherell et al., 2011), participants in ACT group reported greater satisfaction. One challenge in applied research relates to how researchers can identify and separate unique and shared components of these different approaches. However, this is likely to be difficult since ACT is a form of CBT, and therefore is likely to significantly overlap with other underlying therapeutic processes and treatment techniques, such as exposure and behavioural activation (Scott & McCracken, 2015).

A potential fruitful avenue may lay in the analysis of treatment process. For example, an RCT evaluating ACT in chronic whiplash-associated disorder has shown that positive changes in pain-related disability and life satisfaction was mediated by reductions in broader measures of psychological inflexibility (Wicksell, Olsson, & Hayes, 2010) and not by change in one of a number of potentially competing processes, including fear of movement and self-efficacy. However, a recent RCT evaluating traditional CBT has also demonstrated that improvements in pain severity, pain interference, and depression outcomes were mediated by changes in pain acceptance (Åkerblom, Perrin, Fischer, & McCracken, 2015). Overall, it appears at present most chronic pain theories and associated treatments demonstrate similar efficacy, and research comparing dominant approaches is in its infancy.

2.4 Conclusion

This chapter began by summarising the evolution of approaches that led to primary chronic pain conditions being viewed as a multidimensional phenomenon in need of a biopsychosocial perspective. A selection of well-established, empirically supported psychological theories in chronic pain conditions, and their respective psychological constructs, and associated treatments, were discussed. There is currently a wealth of empirical support for psychological theories and associated treatment developments in chronic pain. There are elements from within each of the theories reviewed that appear to be associated with pain severity, pain interference and other relevant functional domains. At least three of these models have resulted in the development of efficacious treatments for chronic pain (McCracken & Morley, 2014; Turk et al., 1983; Vlaeyen & Linton, 2000), demonstrating that targeting specific psychological factors or processes may be an effective way of helping people better manage chronic pain.

All chronic pain models appear to share one limitation. After the contribution of gate control theory (Melzack & Wall, 1965) greater emphasis was placed on developing a "biopsychosocial" model of chronic pain. However, there appears to be distinct lack of specific biological factors or processes embedded within the predominant chronic pain theories, or at least are made less explicit. Whilst recent efforts have been made to link more traditional cognitive behavioural factors or processes of chronic pain to elements of neuropsychology (Jensen, 2010) and neurophysiology (Campbell & Edwards, 2009; Davis & Moayedi, 2013; Edwards, Campbell, Jamison, & Wiech, 2009), it appears chronic pain theories outlined in this chapter do not obviously explain how biological factors interact with psychosocial elements. Whilst the diathesis stress model of MS pain (Kerns, 2000; Kerns et al., 2002) considers the dynamic nature of a person's adjustment in response to a changing neurobiological context, including new or changing symptoms and disease progression, chronic pain theories are yet to clearly incorporate these elements. Another related issue is that chronic pain theories have not distinguished between different types of pain, where most have focused predominantly on musculoskeletal pain. Whilst some researchers have examined the role of psychological factors or processes, and the effects of psychological treatments, in the context of neuropathic pain (Closs, Staples, Reid, Bennett, & Briggs, 2009; Haythornthwaite & Benrud-Larson, 2000; Henwood & Ellis, 2004; Martin, Daniel, & Williams, 2014; McCracken & Yang, 2013), few have directly compared neuropathic

and non-neuropathic pain. Comparing the different types of pain may be helpful to determine whether psychosocial components of existing chronic pain theories can explain neuropathic pain in the context of MS, since it may be it may be the case that the different types of pain lead to different psychological responses, and that psychosocial variables are potentially less relevant in pain of neuropathic origin.

Despite their limitations, the strength of empirical support for second- and third-wave interventions at present appears to be comparable, and the literature offers no clear indication as to whether one chronic pain theory or treatment is necessarily more effective than another, or a combination of approaches. It would therefore appear that all chronic pain theories and frameworks outlined may have some relevance to understanding and treating MS pain. This view is supported by promising preliminary evidence for both CBT and ACT interventions for MS pain outlined in chapter 6. Therefore, at this stage drawing from all chronic pain models and treatment approaches outlined in this chapter is likely to be helpful in guiding our empirical investigations of MS pain and developing a working theoretical model.

To date few attempts have been made to explore the psychosocial correlates of MS pain in a systematic way that considers existing empirical evidence in relation to primary chronic pain models. This makes it difficult to obtain a reliable overall impression of the findings from this growing body of research. A review and synthesis of current research also becomes increasingly important as more studies emerge investigating similar constructs. Therefore, the following chapter presents a systematic review conducted by the author investigating the psychosocial factors or processes associated with pain severity and pain interference in MS. As mentioned previously, these reflect two key clinical outcomes in the chronic pain literature (Dworkin et al., 2008). The purpose of the review was to draw on relevant theory and empirical findings specific to MS to bring together a working model of MS pain, of which key elements are further evaluated in the empirical chapters that follow.

Chapter 3 : A Systematic Review of Potentially Modifiable Psychosocial Factors in MS Pain.

3.1 Chapter overview

This chapter is published in the following article:

Harrison, A.M., McCracken, L.M., Bogosian, A. and Moss-Morris, R. (2015). Towards a Better Understanding of MS Pain: A Systematic Review of Potentially Modifiable Psychosocial Factors. *Journal of Psychosomatic Research*. 78, 12-24.
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3.2 Published article

Title: Towards a Better Understanding of MS Pain: A Systematic Review of Potentially Modifiable Psychosocial Factors

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Key words: Multiple Sclerosis, Pain, Psychosocial, Psychological Factors, Correlate, Systematic Review.

Abstract

Objective: Pain is a common symptom of Multiple Sclerosis (MS). Biomedical treatments achieve only modest reductions in pain severity suggesting this approach may be too narrow. The aim of this systematic review was to assess evidence for associations between modifiable psychosocial factors and MS pain severity and pain interference and use this evidence to develop a preliminary biopsychosocial model of MS pain.

Methods: Empirical studies of pain in MS utilising standardised pain severity and pain interference measures were included. Online databases (Cochrane, PsychInfo, EMBASE, CINAHL, Medline, Web of Science and World Cat) and reference sections of included articles were searched, and corresponding authors contacted to identify unpublished studies. Information about design, sample size, MS type, time since diagnosis, psychosocial and pain measures and key findings were extracted. Thirty-one studies were assessed for quality and a narrative synthesis was conducted.

Results: Similar to primary chronic pain, most studies reported small to medium associations between several psychosocial factors and pain severity and interference. Pain catastrophizing showed consistently strong associations with pain interference. Preliminary findings revealed a strong correlation between pain acceptance and pain interference. However, fear- avoidance appeared less important in MS, and other forms of behavioural avoidance were not explored.

Conclusions: A preliminary model of MS pain outlining specific psychosocial factors is presented with a conceptual formulation from both traditional, and contextual, cognitive behavioural perspectives. Pain catastrophizing, acceptance, and endurance, as opposed to fear avoidance, responses are highlighted as potentially important treatment targets in MS, and directions for future research are outlined.

Introduction

Pain affects around two thirds of people with Multiple Sclerosis (MS) (Nestoriuc & Martin, 2007) and is associated with poor quality of life (Hirsh et al., 2011; Hirsh et al., 2009; Khan, Pallant, Amatya, Young, & Gibson, 2011). Prevalence rates for pain in MS are reported to range from 40-80% (Ehde et al., 2006; Hirsh et al., 2009; O'Connor et al., 2008). This variability may be explained by the divergent definitions of pain used and patient populations studied (O'Connor et al., 2008). A third of people with MS describe pain as one of their worst symptoms (Stenager et al., 1991). People with MS may experience acute or chronic pain (Indaco et al., 1994) arising from multiple aetiologies (Osborne et al., 2007) including neuropathic pain resulting from injury to nerve tissue, musculoskeletal pain related to degenerative muscle or joint dysfunction and migraine headache (O'Connor et al., 2008), which can be neuropathic in origin or secondary to the disease process (Khan & Pallant, 2007; Moisset et al., 2013). Neuropathic pain includes extremity pain, trigeminal neuralgia, Lhermitte's sign and painful tonic spasms including paroxysms. People with MS can experience one or more of these pain syndromes across their disease course (Douglas, Windsor, et al., 2008; Pollmann & Feneberg, 2008), but prevalence does not appear to be associated with age, disease duration (Kerns, 2000) or MS subtype (Archibald et al., 1994; Heckman-Stone & Stone, 2001).

MS pain is typically treated within a biomedical framework. However, a recent review suggests biomedical treatments achieve only modest reductions in pain severity (Beard et al., 2003) and a large proportion of people with MS experience ongoing uncontrolled pain (Kerns et al., 2002). Pain in MS may benefit from a broader conceptualisation including psychosocial factors that may contribute to the experience of pain and incorporating these in treatment approaches. There is at least one proposed biopsychosocial theory of pain-related interference from MS (Kerns, 2000; Kerns et al., 2002). Although an important advance, it draws from a more general model of stress rather than a model or theory developed specifically from empirical data on pain in MS. One way to expand this formulation may be to draw on not only on the empirical MS pain literature, but on the extensive theoretical and empirical literature on primary, non-disease related, chronic pain (Merskey & Bogduk, 1994).

The primary chronic pain literature distinguishes between two key outcomes of pain, the severity of the pain and physical dysfunction, which includes the extent to which pain interferes with activities of daily living, relationships with others and sleep (Turk et al., 2003). These outcomes are considered separately because pain severity only explains some of the variance in the extent to which pain interferes with physical functioning. Physical functioning can also improve even in the absence of improvements in pain severity (Fordyce et al., 1981; Fordyce et al., 1984). Several potentially modifiable cognitive, emotional, behavioural and social factors or processes consistently explain variance in physical functioning over and above pain severity in this group (Jensen, Moore, Bockow, Ehde, & Engel, 2011).

A range of theoretical models exist which attempt to explain how these modifiable psychosocial factors interact to maintain the severity of pain and impact of the pain on physical function (pain interference). Early operant behavioural theory (Fordyce, 1976) highlighted the negative impact of environmental influences (e.g. overly solicitous responses to pain by others) on pain behaviours and outcome. The traditional cognitive behavioural model (Turk, et al. 1983) expanded on operant behavioural theory, suggesting pain-related emotions, beliefs and coping responses (e.g. anxiety, low mood, self-efficacy and perceived social support) also play a crucial role alongside behaviour. Pain catastrophizing, defined as an exaggerated negative orientation toward painful stimuli during actual or anticipated pain experience (Sullivan, 2001), also emerged as a key component of the traditional cognitive behavioural model (Sharp, 2001), and a consistent predictor of outcome. Recent expansions to the traditional cognitive behavioural model include two specific behavioural pathways: The fear-avoidance model (Vlaeyen & Linton, 2000) suggests pain-related fear, defined as interpreting potentially pain-inducing situations as threatening and causing further damage to the body, contributes to hypervigilance, behavioural avoidance and inactivity, resulting in greater pain and interference (Boersma & Linton, 2006; Gatchel et al., 2007). A recent addition to this model suggests another opposing pathway, avoidance-endurance (Hasenbring & Verbunt, 2010), characterized by suppression of pain and increased task persistence, leading to physical overuse and overload, greater anxiety, depression and ultimately reduced functioning.

More recently, contextual cognitive behavioural theory (McCracken, 2006) or acceptance and mindfulness-based 'third-wave' approaches have been applied to

chronic pain (Hayes, Follette, & Linehan, 2004). Influenced by operant behavioural theory and traditional cognitive behavioural model, these draw on six integrated processes within the psychological flexibility model (Hayes, 1999). One process, pain acceptance, defined as willing engagement in activities in a way that includes contact with pain, without defense or attempts to struggle with or control it (McCracken, 2010a, 2010b), has consistently been identified as a key process of change influencing reductions in pain severity and interference (McCracken & Gutiérrez-Martínez, 2011; Vowles, McCracken, & O'Brien, 2011). Although there is no single unifying model of pain, most have reasonable empirical support (Eccleston, Williams, & Morley, 2009; McCracken & Morley, 2014; Morley, Eccleston, & Williams, 1999; Veehof, Oskam, Schruers, et al., 2011). There is also a large body of evidence suggesting therapies based on these theoretical approaches decrease pain severity, disability and related mood disturbance in primary, non-disease-related chronic pain conditions (Eccleston et al., 2009; Veehof, Oskam, Schruers, et al., 2011).

Whilst primary chronic pain may have a different pathophysiology to pain secondary to a neurological condition, exploring psychosocial factors drawn for these models in the context of MS pain will provide insight as to any overlap in these conditions.

The purpose of this study is therefore to identify and systematically review evidence for potentially modifiable psychosocial factors associated with pain severity and pain interference in the MS literature, applying quality ratings when evaluating and interpreting study findings. We refer to pain interference specifically rather than the broader construct of physical functioning as in the context of MS, the latter is potentially effected by a wide range of disease-related symptoms. How these data relate to existing theories of primary chronic pain will be explored and a working theoretical framework of MS pain proposed. Finally, this review will provide directions for future research in this area with a view to refining a psychological treatment approach to pain in MS.

Methods

Criteria for Including Studies within the Review

Studies were included if they met both the following two criteria: (a) Studies of adults with MS experiencing pain and (b) used quantitative, psychometrically validated pain severity and pain interference measures in conjunction with cognitive, emotional, behavioural or social factors/processes typically considered modifiable in the context of cognitive behavioural models of pain and treatment. Studies were also required to either: (c) Explore bivariate relationships between psychosocial factors and pain severity or interference, (d) report multivariate statistical models with psychosocial factors as predictors and pain severity and interference as outcome variables, (e) test group differences, comparing psychosocial variables across pain versus no pain MS groups, or MS pain versus other pain-related conditions, or (f) evaluate treatments for pain in MS looking at psychosocial mediators of improvement in relation to pain severity and interference. Studies were therefore excluded if they failed to meet minimum inclusion criteria (a) and (b), and did not report at least one of the statistical methods described in criteria (c) to (f).

Studies were also excluded if they (a) were not written in English, (b) were non-empirical, general discussion or theoretical papers, (c) used qualitative rather than quantitative methods, (d) included mixed population groups where MS pain-specific data could not be extracted, (e) looked only at quality of life in relation to pain severity and interference, since this may be considered an outcome of pain rather than a modifiable psychosocial factor, (f) reported multivariate statistical models with pain severity and interference as predictors and psychosocial factors as outcome variables.

Selection of Studies

Studies were identified though a systematic online search of CINAHL, Cochrane, EMBASE Medline, PsychInfo, Web of Science and World Cat dissertation databases, contacting key authors and manual searching of reference lists (see flow-chart diagram Fig.1). Database searches were conducted during November 2013 using key search terms outlined in supplementary materials: Appendix A. The first and fourth authors initially screened all online abstracts independently. Relevant full-text articles from both

screens were obtained by the first author and assessed for eligibility, which included both published and unpublished studies. The manual search was conducted by the first author who hand-searched reference lists of all eligible studies at the full-text screening stage, and emailed lead researchers in this area to request any in-press and unpublished studies. Please find all excluded studies at the full text screening stage with reasons in supplementary materials: Appendix B.

Methodological Quality Assessment

The methodological quality of studies was assessed using an adapted version of Ariëns et al's (Ariëns, van Mechelen, Bongers, Bouter, & van der Wal, 2001) quality assessment tool (see supplementary materials: Appendix C). Adapted versions of Ariëns et al's tool have been used across a number of previous reviews (Arden-Close, Gidron, & Moss-Morris, 2008; Bogosian, Moss-Morris, & Hadwin, 2010). Since the tool did not assess methods of statistical analysis and sample characteristics we added items to reflect these domains to meet the needs of this review. The quality assessment tool was composed of eight superordinate methodological categories comprising of 15-items rated as either 'positive' (1) or 'negative' (0) to provide a total positive score. Total scores were classified as poor (0-8, ≤50%) medium (9-12, 60-80%) and good (13-15, ≥80%), reflecting cut-offs used within previous reviews (Arden-Close et al., 2008; Ariëns et al., 2001; Bogosian et al., 2010). The first and fourth authors assessed the studies independently to ensure there was consistency across 10 (30%) of the 31 ratings. Minor discrepancies of 4 ratings were resolved in discussion with the second author until a consensus was reached. The quality assessment of remaining studies was conducted by the first author.

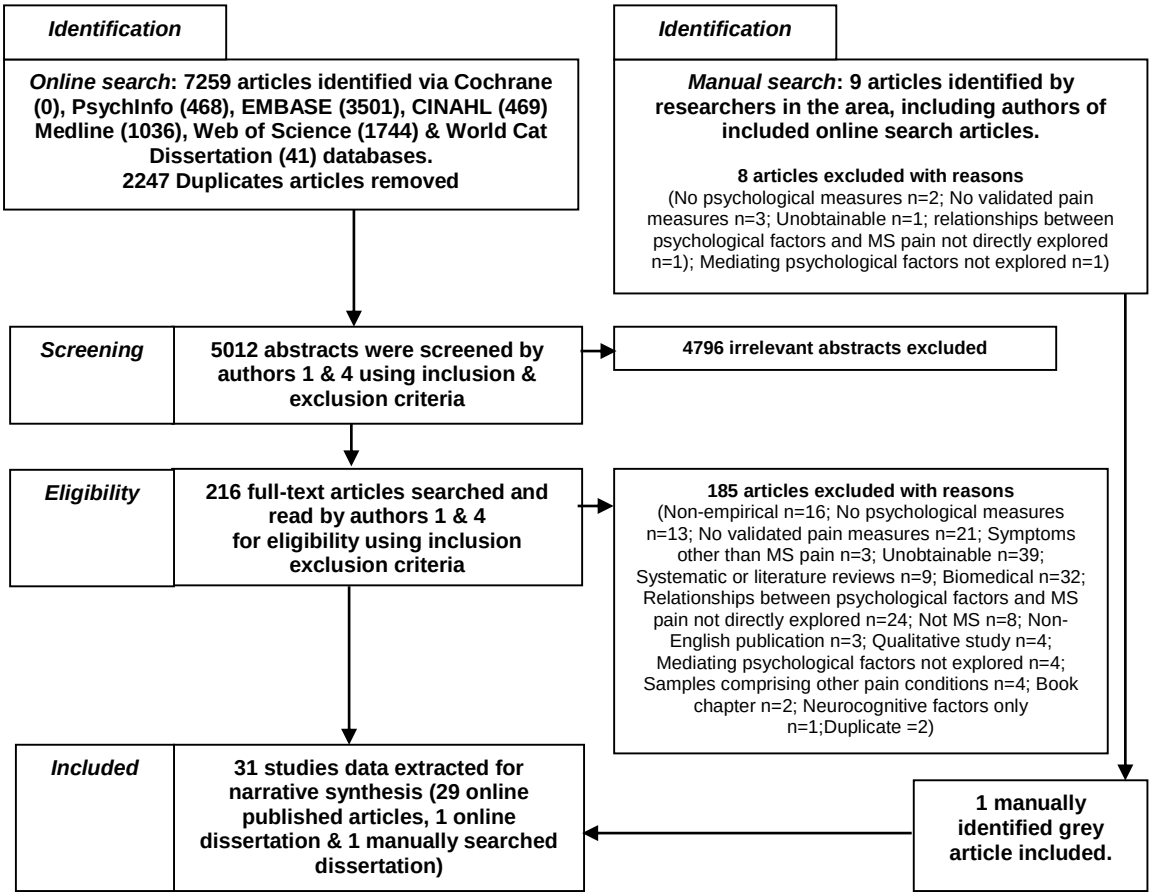


Figure 1 PRISMA Flowchart Diagram

Results

Study Characteristics

The combined search yielded 5012 abstracts, after removing duplicates. Thirty-one studies (29 published and 2 unpublished) were identified as meeting inclusion criteria for this review (Fig. 1) and are summarised in Table 1. Table 2 summarizes the strength of psychosocial factors examined in relation to pain severity and interference measures across these studies. Supplementary materials: Appendix D provides a full summary of the key methodological, demographic and clinical characteristics of included studies.

Data Synthesis

The review question precluded meta-analysis for two reasons. First the broad and multifaceted nature of the review set out to identify a variety of psychosocial factors associated with MS pain severity and interference, rather than focussing on a single

predictor and criterion variable. Eleven psychosocial factors were identified, though different instruments were used to measure the same constructs (see Table 1 footnote and Table 2). Second, studies were characterised by a large degree of methodological, clinical and statistical heterogeneity, sometimes failing to report effect-sizes and measures of variability. Narrative synthesis was used to summarise the data in accordance with Popay et al.'s (Popay et al., 2006) guidance. This involved 1) identifying, listing and tabulating results and organising results with a common statistical rubric, 2) considering factors that might explain any differences in direction and size of effect across the included studies, and 3) assessing the robustness of the synthesis using tabulation and the quality assessment tool and reflecting critically on the synthesis process within the discussion.

In order to address the research aims, potentially modifiable psychosocial factors related to pain severity and interference were identified and grouped. To relate back to existing theories of pain, the results are considered within three sections (see Table 2): (a) Factors related to operant behavioural theory and traditional cognitive behavioural model of chronic pain, (b) Factors related to contextual cognitive behavioural models of chronic pain, and (c) Summary of regression findings.

Where possible bivariate correlations between psychosocial factors and both pain severity and interference will be reported, and interpreted as small, medium and large according to Cohen (Cohen, 1988), Rosnow and Rosenthal's (Rosnow & Rosenthal, 1996) *r* effect-size thresholds. Simple mean score comparisons of psychosocial factors between pain and non-pain MS groups will also be described. Multivariate regressions were not comparable across studies since they controlled for different illness and predictor variables, precluding useful interpretation. However, where bivariate analyses could not be extracted from the papers or through contacting relevant study authors, regression statistics will be presented with a description of type of regression and other control variables. To avoid mixed interpretations regressions will not be presented where pain is the predictor variable and psychosocial factors the outcome.

Table 1 Included Studies

Ref. no. (for Table 2), name, country & date	Study design	MS pain or mixed MS sample & comparator (n)	Recruitment	Pain measures
1. Alschuler et al. USA 2013 (same sample as Kratz et al. 2011)	Cross-sectional	161 (mixed MS)	University of Washington MS research and rehab training centre	Pain severity (0-10 NRS)
2. Brochet et al., France 2009	Longitudinal	69 (mixed MS)	Newly diagnosed community-based patients in Southern France	Pain severity (SEP-59 & NRS)
3. Bruce and Arnett, USA 2009	Cross-sectional	50 (mixed MS) 45 (healthy matched controls)	Recruited from state college or community in in Central Pennsylvania	Pain severity and interference (BPI)
4. Bruce, Polen & Arnett, USA, 2007	Cross-sectional	91 (mixed MS)	MS support groups and the state college in Central Pennsylvania.	Pain severity and interference (BPI)
5. Douglas et al., Australia 2008	Cross-sectional	105 (mixed MS)	Queensland's MS Society database: from a larger study by the authors	Pain severity (Wilkie) Pain Interference (WHOQOL-100)
6. Ehde et al., USA, 2003	Cross-sectional	442 (mixed MS)	MS Association King County, WA.	Chronic Pain Grade (NRS)
7. Glowacka, UK, 2011 (Dissertation)	Cross-sectional	64 (mixed MS)	Internet (advertised on MS Society website)	BPI Modified
8. Grasso et al., Italy, 2008	Cross-sectional	61 (mixed MS) 67 (healthy matched controls)	Outpatient service	Pain severity & interference (MPQ)
9. Hamdy et al. Egypt, 2009	Cross-sectional	49 (headache) 44 (no headache)	Not reported - diagnosed using McDonald Criteria	HSS (1-5 NRS)
10. Holden & Isaac UK, 2011	Cross-sectional	234 (mixed MS) 89 (Rheumatoid Arthritis)	Online self-reported MS diagnosis MS Society UK	Pain severity & interference (MPQ)
11. Kalia and O'Connor, Canada 2005	Cross-sectional	99 (mixed MS)	Outpatients service in Toronto	Pain severity (SF-MPQ)
12. Khan & Pallant, Australia, 2007	Cross-sectional	94 (mixed MS)	Royal Melbourne Hospital database.	Pain severity (SDPS & Chronic Pain Grade)
13. Khan et al., Australia 2011	Cross-sectional	62 (MS pain)	Royal Melbourne Hospital database.	Pain severity (PIR)
14. Kratz et al., USA, 2011	Cross-sectional	114 (mixed MS)	University of Washington MS research and rehab training centre	Pain severity & interference (0-10 NRS)
15. Michalski et al. Germany, 2011	Cross-sectional	38 (mixed MS)	Department of Neurology University of Leipzig	Pain severity 0-10 (NRS: Price et al. 1994)
16. Moisset et al. France 2013	Cross-sectional	673 (mixed MS) 529 (MS pain) of which 346 reported neuropathic pain; 309 migraine headache (ICHD-2)	MS Patients network in Auvergne	Pain severity & interference (BPI) Neuropathic pain severity (DN4)
17. Motl and McAuley, USA, 2010	Longitudinal	291 (mixed MS – ambulatory)	Midwestern chapters of the MS Society.	Pain severity (SF-MPQ)
18. Motl et al. USA 2010	Cross-sectional	269 (mixed MS RRMS only)	National Multiple Sclerosis Society (NMSS	Pain severity and interference combined (SF-MPQ)
19. Motl, Snook & Shapiro, USA 2008	Cross-sectional	133 (mixed MS)	Midwestern chapters of the MS Society.	Pain severity & Interference combined (SF-MPQ)

Table 1 continued

Ref. no. (for Table 2), name, country & date	Study design	MS pain or mixed MS sample & comparator (n)	Recruitment	Pain measures
20. Newland et al. USA, 2005	Longitudinal	247 (MS mixed) 40,907 (Not-MS) long-term care patients	Minimum Dataset (MDS) for residents admitted to community-based long-term care in Missouri	Pain severity (Resident dataset MDS scale referenced)
21. Newland et al. USA, 2009	Cross-sectional	40 (mixed MS – women with RRMS) 40 (healthy controls)	University MS Centre (Mid-West Metropolitan community)	Pain severity & interference (BPI and SF-MPQ)
22. Newland et al., USA, 2012	Cross-sectional	40 (mixed MS – women with RRMS)	Secondary data taken from Newland (2005)	Pain severity & interference (BPI and SF-MPQ)
23. Osborne et al., USA, 2006	Cross-sectional	451 (mixed MS)	Veterans Health Association database	Pain interference (PES)
24. Osborne et al., USA, 2007	Cross-sectional	125 (mixed MS)	MS Society, King County.	Pain severity & interference BPI)
25. Rog et al. UK (2007)	Cross-sectional instrument validation study	141 (MS pain – central neuropathic)	The Walton Centre regional MS clinic	Pain severity for central neuropathic pain (NPS-10)
26. Sasson Gelman, USA, (Dissertation, 2008)	Cross-sectional	1014 (mixed MS)	National MS Society of Greater Washington	Pain interference (BPI)
27. Spain et al Australia 2007	Cross-sectional	687 (mixed MS)	MS Society and outpatient clinics in Victoria	Bodily pain (SF-36)
28. Sullivan and Edgley, Canada, 1992	Cross-sectional	35 (mixed MS) 35 (chronic lower back pain)	Rehabilitation Centre Ottawa (1987-89)	Pain severity (MPQ)
29. Svendsen et al., Denmark 2005	Cross-sectional	50 (MS pain) 50 (MS no pain) 47 (healthy controls)	Previous study in Aarhus county (Svendsen et al 2003)	Pain severity (MPQ-Danish)
30. Tedman, Young & Williams UK 1997	Cross-sectional	92 (MS mixed) 40 (Motor neuron disease)	Walton Centre for Neurology and Neurosurgery	Bodily pain (SF-36)
31. White et al., USA, 2008	Cross-sectional	107 (MS pain)	Mid-Western chapter of the National MS Society	Pain interference (PES)

Pain scales. BPI (Brief Pain Inventory), DN4 (Douleur Neuropathique 4 interview questionnaire), HSS (The intensity of MS-related Headache Scale), ICHD-2 (International Classification of Headache Disorders) MPQ/SF-MPQ (McGill Pain Questionnaire & Short Form Version), NPS-10 (Neuropathic Pain Scale 10-items), NRS (Numerical Rating Scale), PES (Medical outcomes study Pain Effects Scale), PIR (adapted from the Pain Evaluation Questionnaire), SDPS (Simple Descriptive Pain Scale), SEP-59 (Self-administered quality of life questionnaire), SF-36 (Short-Form 36), VAS (Visual Analogue Scale),WHOQOL-100 (World Health Organisation 100).

Psychosocial scales.

1. Perceived social support: CPI (Community Participation Index), MSSS (Medical outcomes Study Modified Social Support Scale).
2. Perceived solicitude: MSPSS (Multidimensional Scale of Perceived Social Support), SOPA (Pain Attitudes Scale).
3. Pain-related self-efficacy and perceived control: CSQ (Coping Strategies Questionnaire), MPRCQ (Multidimensional Pain Readiness to Change Questionnaire), SOPA (Pain Attitudes Scale).
4. Pain-related catastrophizing: CSQ (Coping Strategies Questionnaire), CBSQ (Cognitive and Behavioural Responses to Symptoms Questionnaire), PCS (Pain Catastrophizing Scale).
5. Pain-related fear-avoidance & avoidance, resignation and distraction behaviours: CBSQ (Cognitive and Behavioural Responses to Symptoms Questionnaire), FSR (Pain related behaviour).
6. Pain-related thought suppression: KPI-AEM PCR (Kiel Pain Inventory Avoidance Endurance Questionnaire — Pain-related Cognitive Responses subscale).
7. Illness perceptions: IPQ-R (Illness Perceptions Questionnaire Revised).
8. Pain constancy: PBPI (Pain Beliefs Perception Inventory).
9. Depression: BDI–II (Beck's Depression Inventory), CES-D (Centre of Epidemiological Studies Depression Scale), CMDI (Chicago Multidimensional Depression Inventory), GHQ-28 (General Health Questionnaire), HADS (Hospital Anxiety and Depression Scale), MADRS (Montgomery and Asberg Depression Rating Scale), MDI (Major Depression Inventory), MDS (Resident Minimum Dataset), MHI (Mental Health Inventory), PHQ-9 (Patient Health Questionnaire).
10. Anxiety and worry: HADS (Hospital Anxiety and Depression Scale), MHI (Mental Health Inventory), PSWQ (Pennsylvania State Worry Questionnaire), STAI (State-Trait Anxiety Inventory).
11. Pain-related acceptance: CPAQ (Chronic Pain Acceptance Questionnaire).

Table 1 (continued)

Ref. no. (for Table 2), name, country & date	Psychosocial correlate/predictor measures	Controlled for demographic & disease variables	Key Findings	Quality assessment score (1-15) & major limitations
1. Alschuler et al. USA 2013 (same sample as Kratz et al. 2011)	Depression (PHQ-9)	Chi^2 & Odds Ratio: No	Participants meeting depression criteria were more likely meet pain criteria relative to a non-depressed participant.	10 (Medium) Unclear if groups were matched
2. Brochet et al., France 2009	Depression (MADRS)	Regression: No Odds Ratio: Yes	Depression was worse in the MS pain vs. non-pain group. Depression status at baseline predicted increased risk of pain at two years follow-up.	14 (Good) Unclear if groups were matched
3. Bruce and Arnett, USA 2009	Worry (PSWQ) Depression (CMDI) Anxiety (STAI)	Matching prior to correlation: Yes Regression: Yes but IV & DV opposite to review hypothesis	Excessive worry was associated with greater pain interference (which was higher in the MS group). Chronic worriers endorse more intense pain.	12 (Medium) Sample size was small and no power calculation stated
4. Bruce, Polen & Arnett, USA, 2007	Depression (CMDI and BDI-II)	Bivariate correlation: No Regression: IV & DV opposite to review hypothesis	No direct relationship between pain and depression; with potentially some overlap between the constructs may be present.	14 (Good) No adjustment for correlation
5. Douglas et al., Australia 2008	Pain Beliefs (PBPI), Coping Strategies (CSQ)	Regression: Yes	Pain constancy and perceived ability to reduce pain were strong predictors of pain severity. Pain constancy and pain-related catastrophizing were strong predictors of pain interference.	13 (Good) Unclear if groups were matched
6. Ehde et al., USA, 2003	Depression (CES-D) Anxiety (Prime-MD) Social Support (MSSS)	Fisher's: Yes Regression: Yes	People with MS with pain reported significant higher levels of depression than those without pain. Depression was positively related with pain interference, but not the multivariate level. Perceived social support was not a significant predictor of pain interference.	10 (Medium) Unclear if groups were matched
7. Glowacka, UK, 2011 (Dissertation)	Depression & Anxiety (HADS) Pain Acceptance (CPAQ) Catastrophizing and Fear- avoidance (CBSQ) Thought suppression (KPI-AEM PCR)	Regression: Yes	The predictive role of pain-related cognitions in MS pain interference was only partially confirmed, since pain acceptance remained a significant (strong) predictor when entered into the model, accounting for variance above and beyond other cognitive factors. The remaining factors were highly and positively correlated at the bivariate level.	12 (Medium) Subjects were recruited through the internet (no certainty of MS diagnosis)
8. Grasso et al., Italy, 2008	Depression (MADRS)	Matched for comparison: Yes Regression: No	Depression and gender (i.e. female) were the only strong predictors of pain severity.	12 (Medium) Not advanced statistical methods
9. Hamdy et al. Egypt, 2009	Depression (BDI)	Comparisons: Yes	No significant difference was found in depression scores between patients with migraine and tension headache subgroups.	9 (Medium) No aim or hypotheses
10. Holden & Isaac UK, 2011	Depression (CMDI)	Within MS Comparison: No	Depressed MS participants reported significantly greater pain (combined severity & interference score) compared to non-depressed MS participants.	10 (Medium) Unclear if MS groups were matched

Table 1 (continued)

Ref. no. (for Table 2), name, country & date	Psychosocial correlate/predictor measures	Controlled for demographic & disease variables	Key Findings	Quality assessment score (1-15) & major limitations
11. Kalia and O'Connor, Canada 2005	Depression & Anxiety (HADS)	Bivariate correlation: No	Pain severity was positively correlated with depression and anxiety. When stratified by gender, these correlations were present only in women.	12 (Medium) Unclear if groups were matched.
12. Khan & Pallant, Australia, 2007	Depression (GHQ-28)	Mann Whitney U, Kruskal-Wallis and Chi^2: No	Depression scores did not differ between pain and disability defined groups with MS.	11 (Medium) Classifications obscured the influence of key variables.
13. Khan et al., Australia 2011	Depression (GHQ-28)	Matched cluster comparison: Yes	A 'Dysfunction' cluster had higher levels of pain severity and emotional distress (Depression).	15 (Good) Clusters obscured the influence of key variables.
14. Kratz et al., USA, 2011	Readiness to change Perceived importance Self-efficacy (MPRCQ)	Bivariate correlation: No	Less pain interference was related to self-efficacy and readiness for task persistence at the bivariate level.	14 (Good) Unclear if groups were matched.
15. Michalski et al. Germany, 2011	Pain-related behaviour (FSR)	Matching for ANOVA: Yes	People with MS with pain tended to report increased avoidance and resignation behaviour compared to those without, but this was not statistically significant.	8 (Poor) Very small sample size. No advanced statistics were applied.
16. Moisset et al. France 2013	Pain Catastrophizing (PCS)	Bivariate correlation: No Matching for pain group comparisons: Yes	Pain catastrophizing was strongly correlated with pain severity and pain interference: The non-neuropathic pain subgroup had a larger correlation than those with neuropathic pain.	12 (Medium) Migraine subgroups not matched
17. Motl and McAuley, USA, 2010	Depression and Anxiety (HADS)	Clusters comparison: No	Clusters differed in levels of pain, depression and fatigue. Whereby those with greater pain reported higher levels of depression.	13 (Good) Clusters obscured the influence of key variables.
18. Motl et al. USA 2010	Depression and Anxiety combined score (HADS)	Bivariate correlation: No Structural equation modelling: No	The combined pain severity and interference scores were significantly positively associated with the combined anxiety and depression scores.	12 (Medium) p-values not stated
19. Motl, Snook & Shapiro, USA 2008	Depression (CES-D)	Bivariate correlation: No	Greater depression was significantly associated with greater levels of reported pain (combined score).	13 (Good) No adjustment for correlation
20. Newland et al. USA, 2005	Depression diagnosis (MDS)	Odds ratio: No Chi^2: No Regression: Yes but IV & DV opposite to review hypothesis	The odds of depression in those with pain but not MS were higher than those with MS pain.	13 (Good) MS and Non-MS groups not matched
21. Newland et al. USA, 2009	Depression (BDI-II)	ANOVA: Yes	Women with RRMS and healthy controls did not differ in terms of depression.	9 (Medium) Groups not well matched. Statistical procedures were unclear.

Table 1 (continued)

Ref. no. (for Table 2), name, country & date	Psychosocial correlate/predictor measures	Controlled for demographic & disease variables	Key Findings	Quality assessment score (1-15) & major limitations
22. Newland et al., USA, 2012	Depression (BDI-II)	Cluster comparison: Yes	Clusters differed in levels of pain and depression. Whereby those with more pain experienced greater levels of depression. Greater pain severity was significantly correlated with greater depression.	11 (Medium) The sample size was small relative to variables examined .
23. Osborne et al., USA, 2006	Depression (PHQ-9) Perceived social support (MSSS)	Regression: Yes Bivariate correlation: No	Pain interference was significantly correlated with all psychosocial variables. Depression severity was a strong predictor of pain interference, while perceived social support was not. Depression and pain interference constructs were shown not to overlap.	14 (Good) Normality assumptions were not stated.
24. Osborne et al., USA, 2007	Pain coping (CPCI) Pain attitudes (SOPA) Pain catastrophizing (CSQ) Social Support (MSPSS)	Regression: Yes	Pain severity and interference were positively correlated with catastrophizing. Catastrophizing, illness beliefs and affective, social beliefs and task persistence were strong predictors of pain intensity. Catastrophizing was the only predictor of pain interference. Pain interference was associated with higher levels of perceived solicitude.	14 (Good) Adjustment for demographic and disease variables was not applied.
25. Rog et al. UK (2007)	Depression & Anxiety (HADS)	Correlations: No	Chronic central neuropathic pain severity was associated with higher levels of depression and anxiety in MS.	11 (Medium) Adjustment for demographic and disease variables was not applied.
26. Sasson Gelman, USA, (Dissertation, 2008)	Depression (CES-D) Anxiety (HADS) Perceived Social Support (CPI)	Bivariate correlations: No	Pain interference positively correlated with depression and anxiety, and negatively correlated with perceived social support.	13 (Good) Low response rate and source population not well described.
27. Spain et al Australia 2007	Illness Perceptions (IPQ-R) Anxiety & Depression (HADS)	Regression: Yes	Greater number of MS perceived symptoms (identity), consequences and curability/control of symptoms shared small to medium sized relationships with a combined pain severity and interference score. After controlling for age, MS duration, EDSS and processing speed, depression, and anxiety and identity, timeline and external causes illness perceptions were significant predictors of combined pain severity and interference score.	13 (Good) Response rate not recorded
28. Sullivan and Edgley, Canada, 1992	Coping (modified version of Holahan & Moos, 1987) Depression (BDI-II)	Bivariate correlations: No	Pain severity was associated with greater depression for both the MS and CLBP groups.	13 (Good) The sample size was small relative to variables examined.
29. Svendsen et al., Denmark 2005	Depression (MDI)	ANOVA, Chi^2, t-tests: No	Those with MS pain reported significantly higher depression scores compared to those without pain and healthy controls.	11 (Medium) Risk of error rate from multiple comparisons.

Table 1 (continued)

Ref. no. (for Table 2), name, country & date	Psychosocial correlate/predictor measures	Controlled for demographic & disease variables	Key Findings	Quality assessment score (1-15) & major limitations
30. Tedman, Young & Williams UK 1997	Depression (HADS) Anxiety (HADS)	Bivariate correlations: No	Depression and anxiety were both significantly associated with the combined pain severity and interference score. Patients with motor-neurons disease demonstrated larger negative associations between anxiety, depression and pain.	6 (Poor) Inappropriate statistical methods to compare groups
31. White et al., USA, 2008	Depression & Anxiety (MHI)	Bivariate correlations: No	Pain interference was significantly associated with depression and anxiety.	14 (Good) Adjustment for demographic and disease variables was not applied.

Table 2 Psychosocial factors examined in relation to Pain Severity (PS) and Pain Interference (PI) in MS

Model	Psychological Factor	Quality	Design	Study Ref. (Table 1) and level of statistical techniques applied	Group differences, *r* correlations, odds ratios of PS & PI across studies - Average (range) (n=studies reporting sig.)	ANOVA & Regression (factors in combination with other psychosocial predictors & R^2 range across studies) (n= studies reporting sig.)
Factors from Operant Behavioural and Traditional Cognitive Behavioural Models of Chronic Pain (including Fear-Avoidance and Avoidance-Endurance)	1. Perceived Social Support	Medium Good Good Good	Cross-sectional Cross-sectional Cross-sectional Cross-sectional	6 (PI***) 23 (PI***) 24 (PS* & PI***) 26 (PI*)	PS: -.27 (n=1) PI: -.21 (-.10 to -24) (n=3)	Perceived social support was not a sig. predictor in PI in all multivariable regressions.
	2. Perceived Solicitude	Good	Cross-sectional	24 (PI*)	PI: .29 (n=1)	
	3. Pain-related Self-efficacy and Perceived Control	Good Good	Cross-sectional Cross-sectional	5 (PS*** & PI) 14 (PS & PI*)	PS *r* not stated (n=1) PI: -.32 (-.28 to -.37) (n=1)	Perceived ability to reduce pain alongside pain constancy and were strong predictors of pain severity (n=1).
	4. Pain-related Catastrophizing	Good Medium Good Medium	Cross-sectional Cross-sectional Cross-sectional Cross-sectional	5 (PS*** & PI***) 7 (PI***) 24 (PS*** & PI***) 16 (PS* & PI*)	PS: .31-.54 (n=2) PI: .42 (.41 to .58) (n=3) Neuropathic group: PS: .48 PI: .54 Non-neuropathic group: PS: .61 PI: .64 (n=1) PS: Non-sig.	Catastrophizing predicted 24% alongside other psychosocial variables in PS (n=1). Catastrophizing predicted 11-22% alongside other psychosocial variables in PI. (n=3)
	5. Pain-related Fear-Avoidance	Poor Medium	Cross-sectional Cross-sectional	15 (PS**) 7 (PI***)	PI: .27 (n=1)	PS vs. fear-avoidance ANOVA statistic not reported
	6. Pain-related Thought Suppression	Medium	Cross-sectional	7 (PI***)	PI: .37 (n=1)	Pain-related thought suppression accounted for 14% with other variables in PI but was a non sig. predictor.
	7. Illness Perceptions	Good	Cross-sectional	27 (PS+I***)[4]	PS+I[5] Identity .237 Consequences .389 Control/Curability -.286	Timeline & external causes illness perceptions predicted a further 30% of variance alongside fatigue, depression and anxiety after controlling disease & demographics in PS+I (n=1).
	8. Pain Constancy	Good	Cross-sectional	5 (PS*** & PI***)	PS *r* not stated PI *r* not stated	Pain constancy predicted 26% alongside other psychosocial variables in PS (n=1). Pain constancy predicted 13% alongside other psychosocial variables in PI (n=1).

*Uncontrolled bivariate correlation, uncontrolled comparisons (t-test /chi^2), principle component / cluster analysis
**Controlled bivariate correlation or comparisons, uncontrolled regression analysis
***Controlled multivariate analyses (ANOVA or regression)
[4]PS+PI refers to studies using what appears to be combined pain severity and interference scores
[5]When A.H. contacted this study author to request the PS+I-illness perceptions bivariate correlations, those which were reported as significant were inconsistent with regression findings. This may be attributable to the shared variance within the multivariate equation.

Model	Psychological Factor	Quality	Design	Study Ref. (Table 1) and level of statistical techniques applied	Group differences, *r* correlations, odds ratios of PS & PI across studies - Average (range) (n=studies reporting sig.)	ANOVA & Regression (factors in combination with other psychosocial predictors & R^2 range across studies) (n= studies reporting sig.)
	9. Depression	Medium Good Good Medium Medium Medium Medium Medium Medium Good Good Good Medium Medium Good Medium Good Good Medium Good Medium Good	Cross-sectional Longitudinal Cross-sectional Cross-sectional Cross-sectional Cross-sectional Cross-sectional Cross-sectional Cross-sectional Longitudinal Cross-sectional Longitudinal Cross-sectional Cross-sectional Cross-sectional Cross-sectional Longitudinal Cross-sectional Cross-sectional Cross-sectional Cross-sectional Cross-sectional	1 (PS*) 2 (PS***) 4 (PS & PI*) 6 (PS & PI***) 7 (PI***) 8 (PS*) 9 (Headache PS*) 10 (PS+PI combined*) 13 (PS & PI* cluster) 17 (PS* k cluster) 19 (PS+I combined*) 20 (PS*) 21 (PS* & PI*) 22 (PS* cluster) 23 (PI***) 25 (Central PS*) 26 (PI*) 27 (PS+I combined***) 29 (PS**) 28 (PS*) 30 (PS+I combined*) 31 (PS* & PI*)	PS: .34 (.27 to .38) (n=5) Headache PS: .17 (Non-sig) Central PS: .27 (n=1) Depressed People with MS OR=0.8-2.070 report worse PS than non-depressed (n=3); Depression higher in women with RRMS (n=1) vs. healthy women with and People with MS without pain (n=2). PI: .49 (.28 to .56) (n=4) PS+I Combined: .34 (29-.38) (n=2)	Depression (Log OR) alongside other psychological factors predicted PS (n=1). Depression at inpatient hospital admission was a significant predictor of pain severity at two years follow-up (n=1) Depression alone predicted 13% in PI (n=1); 28% alongside other variables in PI, but was non-sig. Depression predicted a further 30% of variance alongside Illness perceptions, fatigue and anxiety after controlling disease and demographics in PS+I (n=1).
	10. Anxiety and Worry	Medium Medium Medium Good Poor Good	Cross-sectional Cross-sectional Cross-sectional Cross-sectional Cross-sectional Cross-sectional	3 (PS & PI*) 11 (PS*) 25 (Central PS*) 26 (PI*) 30 (PI*) 31 (PI*)	PS: .33 (.26 to .39 to) (n=2) Central PS: .22 (n=1) PI: .36 (.32 to .42) (n=4) PS+I: .32 (n=1)	PI and worry correlation (controlling for state anxiety) was no different to uncontrolled correlation. Anxiety predicted a further 30% of variance alongside illness perceptions, fatigue and depression after controlling disease and demographics in PS+I (n=1).
	Depression & Anxiety (distress score)	Medium	Cross-sectional	18 (PS+I combined*)	PS+I: .42 (n=1)	
Processes from the Contextual Cognitive Behavioural Model of Chronic Pain	11. Pain-related Acceptance	Medium	Cross-sectional	7 (PI***)	PI: -.57 (n=1)	Pain acceptance predicted an additional 4% (unique R^2 change) above all other psychosocial factors in PI (n = 1).

Factors related to Operant Behavioural & Traditional Cognitive Behavioural Models of Chronic Pain

Perceived Social Support and Perceived Solicitude

Within the broader psychological literature (Norris & Kaniasty, 1996) and primary chronic pain models (e.g. operant behavioural (Fordyce, 1976) and traditional cognitive behavioural model (Turk et al., 1983) perceived social support and perceived solicitude have been conceptualized as both helpful and unhelpful psychosocial factors (Cano, 2004a; Cano, 2004b). Solicitous responding is typically defined as a primary reinforcing process by the spouse associated with unhelpful pain behaviours in primary chronic pain conditions (Fordyce, 1976). Perceived solicitousness might therefore be described as the extent to which the pain sufferer believes that others respond to their pain with interest or concern. Perceived social support is defined as the belief that helping behaviors would be provided when needed (Norris & Kaniasty, 1996).

Only one good quality study examined the relationship between perceived social support and pain severity, identifying a non-significant small, negative relationship (Osborne et al., 2007). One medium and three good quality studies found significant small to medium negative associations between perceived social support and pain interference at the simple bivariate level, such that less perceived social support was associated with greater pain interference. Osborne et al (Osborne et al., 2007) also found a medium positive relationship between pain interference and perceived solicitude.

Pain-related Self-efficacy and Perceived Control

Two good quality studies assessed self-efficacy, the extent to which a person sees himself or herself as having the resources available to cope or have control over pain and engage in particular activities. Kratz et al (Kratz et al., 2011), using simple bivariate correlations, found pain self-efficacy to have a non-significant, negative relationship with pain severity, but a small to medium size negative association with pain interference. Similarly, perceived importance and readiness to change (related to healthy exercise behaviour and task persistence) was significantly negatively associated with pain interference but not pain severity.

Pain Catastrophizing

Pain catastrophizing plays a pivotal role in the traditional cognitive behavioural (Sharp, 2001; Turk et al., 1983) and fear-avoidance models of chronic pain (Vlaeyen & Linton, 2000). Two good (Douglas, Wollin, et al., 2008; Osborne et al., 2007) and one medium quality study (Moisset et al., 2013) examined the relationship between pain severity and pain catastrophizing. Two studies found medium to large positive bivariate relationships between pain severity and pain catastrophizing (Moisset et al., 2013; Osborne et al., 2007). Moisset et al's medium quality study also identified similar medium to large positive relationships between pain severity and catastrophizing in both neuropathic and non-neuropathic pain migraine headache subgroups.[4]

In terms of pain interference, the same three studies (Douglas, Wollin, et al., 2008; Moisset et al., 2013; Osborne et al., 2007) and (Glowacka, 2010) looked at the association between pain catastrophizing and pain interference. All four studies reported medium to large positive bivariate associations. Moisset et al (Moisset et al., 2013) also found consistently large positive relationships between pain interference and catastrophizing in both migraine headache neuropathic and non-neuropathic pain subgroups.

Pain-related Fear-Avoidance

Pain-related fear-avoidance is central to the fear-avoidance model of chronic pain (Vlaeyen & Linton, 2000). Two studies explored the relationship between pain-related fear-avoidance and pain severity and interference in MS. A simple bivariate correlation in a medium quality study revealed no relationship between fear-avoidance and pain severity (Glowacka, 2010), but a small positive relationship with pain interference. In contrast, Michalski et al's (Michalski et al., 2011) low quality study compared self-reported pain-related fear-avoidance behaviours between two MS groups. People with MS with pain reported a significantly greater tendency to engage in avoidance and resignation behaviours than those without pain.

[4] Classified as probable and chronic migraine headaches based on the second edition of the International Classification of Headache Disorders (ICHD-2), and assessed as having neuropathic and/or non-neuropathic characteristics using the Douleur Neuropathique 4 interview questionnaire (DN4).

Pain-related Thought-Suppression

Pain-related thought suppression is a central construct of the avoidance-endurance model of chronic pain (Hasenbring & Verbunt, 2010). One medium quality study (Glowacka, 2010) found a medium size positive correlation between thought suppression and pain interference at the simple bivariate level, such that greater thought suppression was associated with greater pain interference.

Illness and Symptom Perceptions

Illness perceptions are a core component of the common sense model of illness representations (Leventhal et al., 1984). While no chronic pain theory explicitly includes illness perceptions, they have been incorporated into traditional cognitive behavioural interventions for other MS symptoms and are often addressed in CBT approaches for pain (Knoop et al., 2012). The model assumes each patient has their own ideas about the identity, cause, timeline, and consequences of their illness and symptoms, which may ultimately influence their ways of coping and outcome. One good quality study (Spain, Tubridy, Kilpatrick, Adams, & Holmes, 2007) found small to medium size relationships between high identity (the number of symptoms the patient attribute to their MS), low control/cure (beliefs about whether one's own actions or medical treatment can influence the disease) and high consequences (beliefs about the negative consequences of MS) and a combined pain severity and interference score.

Pain constancy, the temporal belief that pain will be enduring (Williams, Robinson, & Geisser, 1994), is similar to the concept of chronic timeline defined in the common sense model. One good quality study (Douglas, Wollin, et al., 2008) explored the relationship between pain constancy, pain severity and interference. A regression analysis found, amongst other psychosocial variables, pain constancy was the strongest positive predictor of pain severity and pain interference ratings, accounting for 26% and 13% of the variance respectively. Both models controlled for demographic factors, and pain severity when investigating pain interference.

Depression

Depression was a common factor investigated in relation to pain severity and interference, occurring in a total of twenty-one included studies (twelve medium and nine good in quality). Twelve studies explored the relationship between depression and pain severity, and seven pain interference. Three studies also investigated depression in relation to a combined pain severity and interference total score.

In terms of pain severity, two medium and one good quality study demonstrated small to medium size positive relationships between depression and pain severity using simple bivariate correlations (Kalia & O'Connor, 2005; Newland et al., 2012; Sullivan et al., 1992). One medium quality study looking exclusively at neuropathic MS pain (Rog et al., 2007) demonstrated the same result. However, a good quality study (Bruce, Polen, & Arnett, 2007) conducted a partial correlation controlling for MS-related disability found that depression (using the BDI-II) and pain severity were unrelated. One medium quality study (Kalia & O'Connor, 2005) examined correlations for each gender and found that only women had a significant medium size positive relationship between depression and pain severity. One medium quality study (Hamdy, Amer, Ramzy, Rabah, & Ashour, 2009) showed that headache severity and depression (BDI-II) were unrelated. In terms of odds ratios, one medium (Alschuler et al., 2013) and one good quality study (Brochet et al., 2009) showed MS participants meeting depression criteria were 1.196–2.070 times more likely to meet pain criteria (greater severity) relative to non-depressed MS participants.

Six studies applied statistical comparisons. Three medium (Brochet et al., 2009; Ehde et al., 2003; Svendsen, Jensen, Hansen, & Bach, 2005) and one good (Newland, Wipke-Tevis, Williams, Rantz, & Petroski, 2005) quality study indicated people with MS with greater pain severity had significantly higher levels of depression compared to matched people with MS with no pain, and healthy controls. However, one medium quality study showed levels of depression did not significantly differ between women with relapsing-remitting MS who experienced pain with healthy controls (Newland et al., 2009). Furthermore, one medium quality study (Hamdy et al., 2009) found no significant differences in self-reported depression between MS migraine and tension-like headache subgroups. One poor quality study found that patients with motor-neurons disease

demonstrated larger associations between pain severity and depression when compared to people with MS (Tedman, Young, & Williams, 1997).

In terms of pain interference, three good and one medium quality study indicated a medium to large positive relationship between depression and pain interference at the simple bivariate level (ranging from *r* = .28 to .60) (Glowacka, 2010; Osborne, Turner, et al., 2006; Sasson Gelman, 2009; White et al., 2008).

Depression was investigated in relation to a combined pain severity and interference total score in one poor (Tedman et al., 1997), one medium (Holden & Isaac, 2011) and two good quality studies (Motl, Snook, & Schapiro, 2008; Spain et al., 2007). Two studies (Motl et al., 2008; Tedman et al., 1997) indicated a small to medium positive relationship between depression and pain severity and interference total score, ranging from *r* = .29-.38. Holden et al (Holden & Isaac, 2011) found depressed MS participants reported significantly greater pain severity and interference total scores compared to non-depressed MS participants $p<0.001$).

Anxiety & Worry

Three medium quality studies (Bruce & Arnett, 2009; Kalia & O'Connor, 2005; Rog et al., 2007) examined relationships between chronic worry and anxiety and pain severity. While two studies (Bruce & Arnett, 2009; Rog et al., 2007) found small positive correlations (*r* = .22 and .26), one (Kalia & O'Connor, 2005) identified a significant medium correlation, along with a larger relationship for females when stratified by gender.

The relationship of chronic worry and anxiety with pain interference was explored in one poor, one medium and two good quality studies (Bruce & Arnett, 2009; Sasson Gelman, 2009; Tedman et al., 1997; White et al., 2008). All studies consistently demonstrated significant medium size positive relationships between chronic worry and anxiety and pain severity at the simple bivariate level (ranging from *r* = .32 to .42). Bruce et al (Bruce & Arnett, 2009) also used a partial correlation to control for trait anxiety in relation to interference, which did not alter the initial correlation.

A single medium quality study (Motl et al., 2010) identified a medium size positive correlation (r = .42) between a combined depression and anxiety total score and a combined pain severity and interference total score.

Factors from the Contextual Cognitive Behavioural Model of Chronic Pain

Pain Acceptance

One medium quality study (Glowacka, 2010) demonstrated a large negative relationship between the pain willingness component of the Chronic Pain Acceptance Questionnaire (CPAQ) and pain interference at the bivariate level.

Summary of Regression Findings

A number of cross-sectional studies identified associations between pain severity, interference and psychosocial variables using multivariate models. Other than perceived social support and solicitude (Ehde et al., 2003; Osborne et al., 2007; Osborne, Turner, et al., 2006), all psychosocial predictors within regression models, usually in conjunction with other psychosocial factors, were significant, accounting for between 4-30% of the variance in pain severity and pain interference (Brochet et al., 2009; Douglas, Wollin, et al., 2008; Glowacka, 2010; Osborne et al., 2007; Spain et al., 2007). All studies (see Table 2) controlled for demographic and disease factors, while three controlled for pain severity when pain interference was the entered as the outcome variable (Douglas, Wollin, et al., 2008; Glowacka, 2010; Osborne et al., 2007).

Discussion

Overall Completeness and Applicability of the Evidence

The purpose of this systematic review was to identify and assess quality of studies looking at potentially modifiable psychosocial factors associated with MS pain severity and interference and synthesise the evidence. Thirty-one studies, most of medium to good quality, offer preliminary support for the presence of several treatment modifiable psychosocial factors related to MS pain.

In most instances, in line with the primary chronic pain literature (Jensen, Moore, et al., 2011), correlations between a range of psychosocial factors and both pain severity and interference were similar in size. Consistent with traditional cognitive behavioural and fear-avoidance chronic pain theories, studies reported small to medium relationships between greater anxiety, depression, greater tendency to attribute a wide range of symptoms to MS, beliefs about pain constancy, the uncontrollable and serious nature of MS and increased pain severity and interference. Pain catastrophizing consistently demonstrated a medium to large relationship with pain interference at the bivariate and multivariate level. This is consistent with a recent study combining MS with other illness groups, which showed that pain catastrophizing was a significant predictor of pain severity and interference after controlling for diagnostic groups (Hirsh et al., 2011). Pain-related thought suppression shared a medium association with pain interference but was not examined in relation to pain severity. Reduced self-efficacy was only related to greater pain interference. Smaller and less consistent associations were reported in studies looking at relationships between perceived social support, the belief that others should respond solicitously and pain outcome, with perceived support having a positive effect on pain outcome and solicitousness a negative effect.

Most MS studies incorporated variables drawn from the traditional cognitive behavioural and fear-avoidance perspective. One unpublished study focused on variables relevant to the contextual cognitive behavioural model. Findings from this single study indicated pain acceptance had a strong relationship with pain interference and, unlike most factors above, was negatively associated with pain interference, having a protective role. The relationship between acceptance and pain severity was not examined. Findings from a recent study of patients with chronic pain secondary to neurological conditions, including MS (Kratz, Hirsh, Ehde, & Jensen, 2013), showed pain acceptance predicts less pain interference and depression, and greater social role satisfaction and quality of life. This is consistent with Pakenham (Pakenham & Fleming, 2011) and Ferenbach's unpublished study (Ferenbach, 2011) showing that general acceptance, alongside other contextual cognitive behavioural processes, is associated with better adjustment in MS.

Taken together, this review suggests a number of cognitive factors appear relevant to MS pain. However, there was only tentative evidence for the relationship between fear-avoidance, a core component of primary chronic pain models and pain severity. Fear-

avoidance shared a small positive relationship with pain interference, in a relatively small unpublished study (Glowacka, 2010). The same study, found a stronger relationship between higher levels of pain-related thought suppression and greater pain interference. It is possible that people with MS overall are generally less fear avoidant, and instead, have a greater tendency to engage in pain-related avoidance-endurance behaviours consistent with the avoidance-endurance model (Hasenbring & Verbunt, 2010). Alternatively, these findings might suggest there is a smaller subgroup of pwMS who experience pain-related fear. However, since review findings are preliminary, and fear avoidance is a consistent predictor of outcomes in primary chronic pain conditions (Crombez et al., 2012), it would be helpful to determine its relevance to MS pain in future research.

Preliminary findings for the relationship between psychosocial factors and MS pain from different aetiologies were identified. One study (Rog et al., 2007) identified a small to medium size association between *central neuropathic* pain severity, depression and anxiety. Another study (Moisset et al., 2013) demonstrated large positive correlations between pain catastrophizing and pain severity and pain interference in both neuropathic and non-neuropathic subgroups. Moisset et al (Moisset et al., 2013) also found those with migraine headache reported greater pain severity, interference and pain catastrophizing compared to those with tension headache. In terms of disease characteristics, only one study looked at relapsing-remitting disease (Newland et al., 2009) but no other subtypes. Therefore, clarifying potential differences between painful syndromes and MS subtypes in relation to psychosocial factors may also be helpful to guide treatment development.

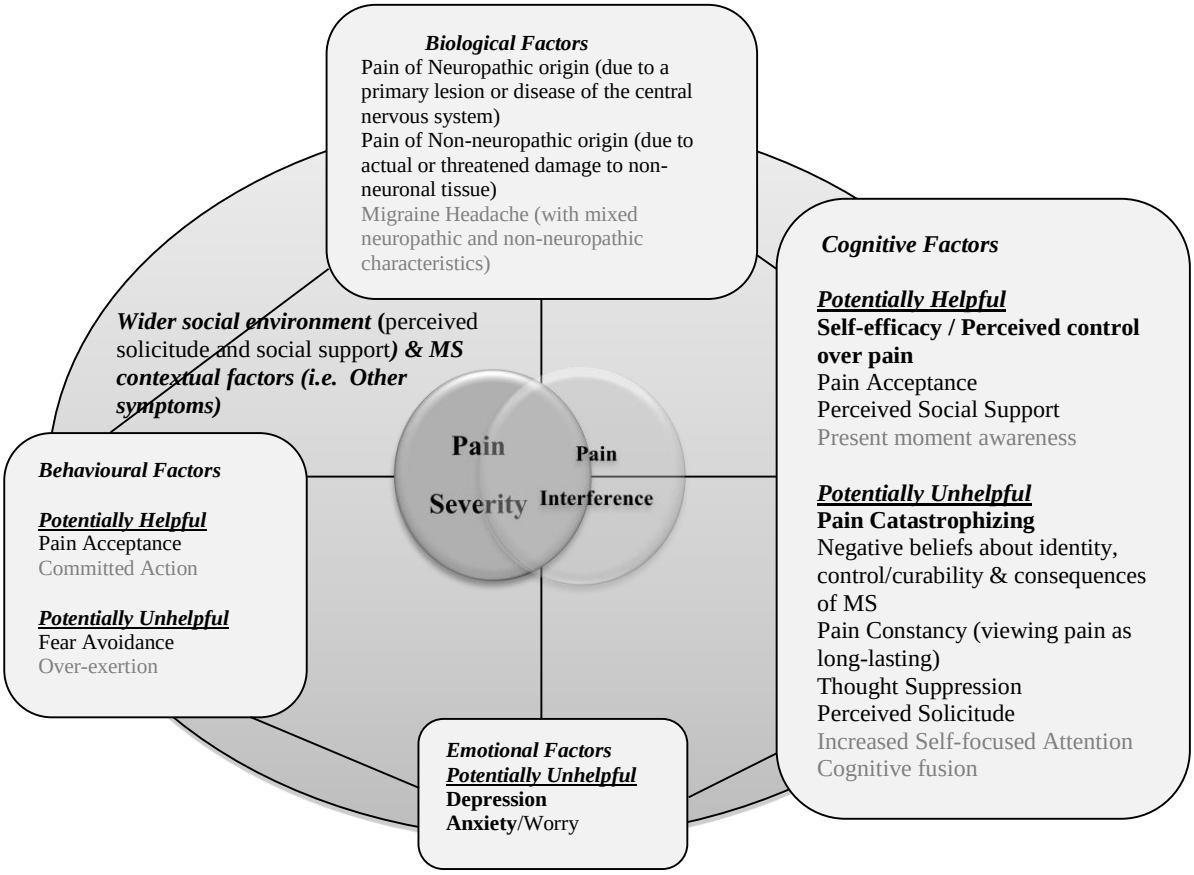
Preliminary Conceptual Model

In Figure 2 we outline a working conceptual model of MS pain to inform future research and interventions in this area. Our model expands on Kerns' biopsychosocial diathesis stress model of MS pain (Kerns et al., 2002) by specifying the psychosocial factors that may be important in magnifying or perpetuating the pain and associated disability. In particular, the figure elaborates on cognitive, emotional, behavioural and social factors or processes related to pain severity and interference, informed by empirical studies. These factors derive from well-established, empirically supported psychological theories and treatments within primary chronic pain. As with Kerns'

conceptualisation, our model argues that biological factors, including neuropathic and musculoskeletal processes, medication and other painful syndromes unrelated to MS, interact with psychosocial elements in contributing to both pain severity and interference. Where relevant, factors have been further divided into helpful or unhelpful in terms of their influence on pain severity and pain interference. These biospychosocial factors sit within a context of predisposing experience, current MS symptoms and the social environment. While reviewed studies suggest psychosocial factors associated with MS pain are similar to other chronic pain populations, it is important to acknowledge the wider interactive context of pain in relation to other inherently painful (e.g. optic neuritis and spasticity) or non-painful MS symptoms (e.g. fatigue and immobility). As one example, MS fatigue is also associated with a variety of unhelpful potentially modifiable psychosocial responses (Knoop et al., 2012). Like Kerns, our model also recognises pain can potentially be exacerbated by use and overuse of both generic MS treatments (e.g. steroids) and medications prescribed for pain-relief.

The model also attempts to integrate the traditional cognitive behavioural and contextual cognitive behavioural approaches in relation to our findings. From a traditional cognitive behavioural perspective, an unhelpful catastrophic response, or belief that pain will persist no matter what, may lead to the experience of worry, anxiety and depression and inward self-focus behaviours. It may be that the nature of avoidance for the majority of people with MS reflects "endurance", comprising thought-suppression and regular over-exertion, as opposed to fearful withdrawal or deactivation responses. As indicated in grey, it is important to note that few MS studies have specifically explored other forms of avoidance behaviours (Hasenbring & Verbunt, 2010) (except avoidance in the context of fear), and are hypothesised behaviours drawn from studies of people with primary chronic pain. It was also the case that few studies examined social factors in relation to pain. From a contextual cognitive behavioural psychological flexibility perspective, the observed role of pain catastrophizing and fear, thought suppression and overexertion might reflect a broader pattern of experiential avoidance. Being the opposite of avoidance, pain acceptance has a significant behavioural component and, therefore, is represented as both a cognitive *and* behavioural process in our model. An individual's unwillingness to have pain (non-acceptance), alongside their inability to de-literalise from pain-related thoughts and associated distress (cognitive fusion), may result in a lack of present moment awareness. This may lead to repeated failed attempts to control or reduce pain, to the exclusion of

pursuing valued life activities (committed action). In either conceptualisation, this may ultimately lead to greater pain severity and pain interference, physical and social deconditioning, anxiety and depression. More work in MS is needed to clarify these relationships.



Bold text = strong evidence, with many studies conducted with studies consistently supporting this role.
Normal text = weaker evidence, where findings appear to be consistent but studies are few.
Grey text **=** factors that may play an important role in primary chronic pain theories but have not been investigated.
The above maintenance model is assumed to be interactional rather than unidirectional

Figure 2 Preliminary Conceptual Model of MS Pain

Implications for Therapy

Given that our current MS findings show only few differences from those with primary chronic pain conditions, it may be that current psychological treatments offered to primary chronic pain patients (Eccleston et al., 2009; Veehof, Oskam, Schruers, et al., 2011) may equally translate to improved functioning for people with MS. However, the potential differences observed in fear-avoidance may have implications for the goals of treatment, such that fear-avoidance therapeutic techniques may fit less well to people

with MS. There are at least two possible current cognitive behavioural approaches in pain management, traditional cognitive behavioural (CBT) and contextual cognitive behavioural therapy, or Acceptance & Commitment Therapy (ACT). Despite having divergent scientific principles, both therapies aim to address cognitive and emotional facets of chronic pain and disability, albeit using different approaches. In CBT, unhelpful thoughts and behaviours are replaced with more helpful alternatives. In ACT thoughts are viewed functionally and their functions are targeted for change, such as whether they are followed or allowed to exert influence. ACT aims to loosen the exclusive influences of thoughts over behaviour patterns and to increase the influence of direct features of the situation at hand and one's goals and values. Considering which of these processes are more amenable to change and likely to have the greatest positive benefit for people with MS is important, as is the question of which will lead more easily to future treatment developments. Overall, the similarities and differences outlined between CBT and ACT are not merely semantic, since they inform how the clinician encourages the patient to approach the problem of pain and the design of future interventions.

Preliminary therapy trials in MS indicate both approaches may have value in managing pain in MS. A small uncontrolled trial of a cognitive restructuring hypnotic intervention for MS was associated with significant reductions in catastrophizing, pain intensity and interference (Jensen, Ehde, et al., 2011). A recent uncontrolled pilot trial of ACT for MS was associated with a reduction in thought-suppression and pain interference (Sheppard, Forsyth, Hickling, & Bianchi, 2010). While two RCTs assessing the efficacy of CBT interventions for people with MS are underway (Ehde, unpublished; Kerns, unpublished), more theory-based developments are needed. By defining key therapeutic mechanisms, and testing mechanisms of change in larger trials, we will be able to refine our conceptual model and key processes to address in future MS pain interventions.

From the point of view of care providers, it may also be important to understand how pain interacts with other MS symptoms (e.g. ambulation, fatigue and sleep) within a multi-morbid, integrated biopsychosocial model that informs the development of treatment aiming to improve symptom management more generally.

Limitations and Directions for Future Research

This review is limited by the cross sectional nature of the studies so the direction of the relationships between pain and modifiable psychosocial factors is unclear. The focus on bivariate findings and the potential for confounding in relation to disease severity means interpretation ought to be met with a degree of caution.

The reviewed studies had several limitations. While three studies (Brochet et al., 2009; Motl & McAuley, 2010; Newland et al., 2005) provided longitudinal evidence investigating trends in people with MS pain-related depression and anxiety over time, studies investigating other psychosocial factors were mostly cross-sectional, limiting causal interpretation. Nevertheless, studies were helpful in identifying factors as relevant targets for psychological interventions as relationships can be reciprocal.

Small sample sizes may have limited the ability to detect relationships (Bruce et al., 2007; Glowacka, 2010; Michalski et al., 2011; Newland et al., 2012; Sullivan et al., 1992), while better powered studies sampled US male military veterans, a non-generalizable cohort not reflecting the higher prevalence of women observed in epidemiological studies (Alonso & Hernán, 2008; Compston & Coles, 2008).

Most studies did not refer to a psychological theory or hypothesis as a rationale for selecting psychosocial factors, making it difficult to derive a consistent picture of how constructs are theoretically related and which may be most important. In this paper, we have proposed a conceptual model to help structure future work in this area. Future research should include large samples so that associations and multiple pathways can be reliably tested. No studies examined psychosocial differences across MS subtypes, and few explored whether there are differences between neuropathic and non-neuropathic pain. Once a clear theory base is developed, interventions can be designed accordingly and tested in randomised controlled trials (RCTs). RCTs should examine not only pain outcomes but also mechanisms of action by taking into account potential mediating and moderating psychosocial factors. These process analyses can then feedback and if necessary modify the original theory.

Acknowledgements

The authors express thanks to the MS Society for funding this research.

Supplementary Materials: Appendix A: Search Strategies

Cochrane, Embase, Medline, CINAHL, PsychInfo & Web of Science November 2013

Terms followed by "/" are MeSH terms.

MS search terms*:*

1. exp Multiple Sclerosis/
2. Multiple Sclerosis.mp
3. MS.mp
4. Demyelinating disease.mp
5. Disseminated sclerosis.mp
6. Encephalomyelitis disseminate.mp
7. Or/1-6

Pain search terms:

1. exp Pain/
2. Pain.mp
3. Dysesthetic.mp
4. Lhermitte's sign.mp
5. Trigeminal Neuralgia.mp
6. Low$ Back Pain.mp
7. Muscle spasms.mp
8. Tonic Spasms.mp
9. Headache.mp)
10. Or/8-16

Psychosocial correlate terms:

18. Psycholog$.mp
19. Psychosocial factors/
20. Psychological factors.mp
21. Adjustment.mp
22. Depression.mp
23. Anxiety.mp
24. exp mood/ (PsychInfo, Emotional states/; Medline Affect/ (restricted to classification)
25. exp Social adjustment/
26. Social function$.mp
27. exp Quality of Life/
28. Coping.mp
29. Belief$.mp
30. Cognition.mp
31. Perception.mp
32. Fear avoidance.mp
33. Interference.mp
34. Catastrophi?ing.mp
35. Acceptance.mp
36. Willingness.mp
37. Mindfulness.mp
38. Endurance.mp
39. Model
40. Biopsychosocial
41. Or/18-40

Supplementary Materials: Appendix A Search Strategies (Continued)

Web of Science November 2013

Topic=(Multiple Sclerosis OR MS OR Demyelinating disease OR Disseminated sclerosis OR Encephalomyelitis disseminate) AND Topic=(Pain OR Dysesthetic OR Lhermittes sign OR Trigeminal Neuralgia OR Low$ Back Pain OR Muscle spasms OR Tonic Spasms OR Neuropathic pain OR Headache) AND Topic=(Psycholog$ OR Psychosocial factors OR Psychological factors OR Adjustment OR Depression OR Anxiety OR Mood OR Social adjustment OR Social function OR Quality of Life OR Coping OR Belief OR Cognition OR Perception OR Fear avoidance OR Interference OR Catastrophi?ing OR Acceptance OR Willingness OR Mindfulness OR Endurance) OR Model OR Biopsychosocial

Refined by: Document Type=(ARTICLE) AND Languages=(ENGLISH)

Timespan=All Years. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH.

Lemmatization=On

World Cat Search November 2013

Keywords: kw:Multiple Sclerosis kw:Pain OR Dysesthetic OR Lhermitte's sign OR Trigeminal Neuralgia OR Lower Back Pain OR Muscle spasms OR Tonic Spasms OR Neuropathic pain OR Headache OR Severity OR Intensity kw:Psycholog$ OR Psychological factors OR Adjustment OR Emotional Response OR Depression OR Anxiety OR Fear avoidance OR Interference OR Catastrophizing OR Acceptance OR Willingness OR Mindfulness OR Endurance OR Coping beliefs OR Cognition OR Perception OR Model OR Biopsychosocial

Article/Chapter

Thesis/dissertation

Language: English

Non-Juvenile

Supplementary Materials: Appendix B Table of excluded studies

First online abstract screen by authors 1 & 4

7259 after removing 2247 duplicates = 5012 abstracts. 4796 were irrelevant and so excluded:

Second online full paper sought to be screened by authors 1 & 4

Of 216 *k*=185 were excluded + 8 manually identified articles = 192 (references listed below):

Total/Online/Manual Full article exclusions with reasons:

Non-empirical *k*=16/16/0
No psychological measures *k*=15/13/2
No validated pain measures *k*=24/21/3
Symptoms other than MS pain *k*=3/3/0
Unobtainable k=40/39/1
Systematic or literature reviews *k*=9/9/0
Biomedical *k*=32/32/0
Relationships between psychological factors and MS pain not directly explored *k*=25/24/1
Not MS *k*=8/8/0
Non-English publication *n*=3/3/0
Qualitative study *n*=4/4/0
Mediating psychological factors not explored *n*=5/4/1
Samples comprising other pain conditions *n*=4/4/0
Book chapter *n*=2/2/0
Neurocognitive factors only *n*=1/1/0
Duplicate *k* =2/2/0

Grand Total of included studies *k*= 31

No.	Study Reference	Exclusion Basis	Comments
1	Anagnostou E and Mitsikostas D. Time perception in migraine sufferers: An experimental matched-pairs study. Cephalalgia. 2005; 25: 60-7.	**Not MS Population**	
2	Al-Smadi J, Warke K, Wilson I, et al. A pilot investigation of the hypoalgesic effects of transcutaneous electrical nerve stimulation upon low back pain in people with multiple sclerosis. Clinical Rehabilitation. 2003; 17: 742-9.	Biomedical	
3.	Alschuler, K. N., Ehde, D. M., & Jensen, M. P. (2013). Co-occurring Depression and Pain in Multiple Sclerosis. *Physical Medicine and Rehabilitation Clinics of North America*.	Review	
4.	Alschuler, K. N., Jensen, M. P., & Ehde, D. M. (2012). The Association of Depression with Pain-Related Treatment Utilization in Patients with Multiple Sclerosis. *Pain Medicine*, *13*(12), 1648-1657.	Relationships between psychological factors and MS pain not explored	
5.	Alschuler, K. N., Jensen, M. P., & Ehde, D. M. (2012). Defining mild, moderate, and severe pain in persons with multiple sclerosis. *Pain Medicine*, *13*(10), 1358-1365.	No psychological measures	
6.	Archibald, C. J., P. J. McGrath, et al. (1994). "Pain prevalence, severity and impact in a clinic sample of multiple-sclerosis patients." Pain 58(1): 89-93.	Relationships between psychological factors and MS pain not explored	Nor use of NRS, VAS pain severity and interference measures
7	Armutlu, K., M. Kerem, et al. (2002). "Pressure pain in multiple sclerosis patients and in healthy subjects." Pain Clinic 14(2): 147-151.	MS pain but biomedical	
8	Bagnato F, Centonze D, Galgani S, Grasso MG, Haggiag S and Strano S. Painful and involuntary multiple sclerosis. Expert Opinion on Pharmacotherapy. 2011; 12: 763-77.	Biomedical review	
9	Bagsic-Kes V, Bosnjak-Pasic M and Demarin V. Pain syndromes in patients with multiple sclerosis. Acta Clinica Croatica. 2007; 46: 331-3.	Biomedical	

10	Barwick, F., P. Arnett, et al. (2009). "Managing Pain in Multiple Sclerosis: the Role of Sleep, Coping, and Quality of Life." Archives of Clinical Neuropsychology 24(5): 526-526.	*Unobtainable - Abstract available only*	No email address located
11	Beiske AG, Pedersen ED, Czujko B and Myhr KM. Pain and sensory complaints in multiple sclerosis. European Journal of Neurology. 11 (7) (pp 479-482), 2004. Date of Publication: July 2004.	Biomedical	
12	Beiske, A., E. Svensson, et al. (2008). "Depression and anxiety amongst multiple sclerosis patients." European Journal of Neurology 15(3): 239-245.	Not a validated pain measurement	
13	Bermejo, P. E., C. Oreja-Guevara, et al. (2010). "[Pain in multiple sclerosis: prevalence, mechanisms, types and treatment]." Revista de Neurologia 50(2): 101-108.	Not written in English	
14	Borgel F. Pain and early stage of multiple sclerosis. Revue Neurologique. 2009; 165: S129-S34.	*Unobtainable - Abstract available only*	
15	Borsook D. Neurological diseases and pain. Brain. 2012; 135: 320-44.	Biomedical review	
16	Brochet B, Boukari S, Deloire M, Salort-Campana E, Bonnet M and Petry KG. Pain and pain-related quality of life at the early stages of multiple sclerosis. Multiple Sclerosis. 2006; 12: S31-S2.	Duplicate - Conference abstract of the same included study	
17	Bruce, J. M. (2006). "The relationship between pain, emotional memory, and depression in a sample of patients with multiple sclerosis." Dissertation Abstracts International: Section B: The Sciences and Engineering 66(8-B): 4474.	*Unobtainable - Abstract available only*	No funding to enable purchase on pro-quest thesis.
18	Buchanan, R. J., S. J. Wang, et al. (2001). "Profiles of nursing home residents with multiple sclerosis using the minimum data set." Multiple Sclerosis 7(3): 189-200.	Relationships between psychological factors and MS pain not explored	
19	Buchanan RJ, Martin RA, Wang S and Ju H. Analyses of nursing home residents with multiple sclerosis at admission and one year after admission. Multiple Sclerosis. 10 (1) (pp 74-79), 2004. Date of Publication: February 2004.	Pain not measured in conjunction with psychological measures	
20	Buchanan, R. J., S. Wang, et al. (2003). "Analyses of nursing home residents with multiple sclerosis and depression using the Minimum Data Set." Multiple Sclerosis 9(2): 171-188.	No pain measurements	
21	Buchanan RJ, Martin RA, Zuniga M, Wang SJ and Kim M. Nursing home residents with multiple sclerosis: comparisons of African American residents to white residents at admission. Multiple Sclerosis. 2004; 10: 660-7.	Pain not measured in conjunction with psychological measures	
22	Buchanan RJ, Wang S and Ju H. Gender analyses of nursing home residents with multiple sclerosis. Journal of Gender-Specific Medicine. 6 (2) (pp 35-46), 2003. Date of Publication: 2003.	*Unobtainable*	
23	Buchanan RJ, Wang S and Ju H. Analyses of the minimum data set: comparisons of nursing home residents with multiple sclerosis to other nursing home residents. Multiple Sclerosis. 2002; 8: 512-22.	Pain not measured in conjunction with psychological measures	
24	Chatel, M., M. Lanteri-Minet, et al. (2001). "[Pain in multiple sclerosis]." Revue Neurologique 157(8-9 Pt 2): 1072-1078.	Not Empirical	
25	Churyukanov MV, Alekseev VV, Kukushkin ML, Krupina NA, Toropina GG and Yakhno NN. Clinical, psychological and neurophysiological aspects of central pain syndrome in multiple sclerosis. European Journal of Pain Supplements. Conference: 7 Congress of the European	*Unobtainable - Conference Abstract only*	Emailed and awaiting response

	Federation of Pain Chapters: Pain in Europe VII, EFIC Hamburg Germany. Conference Start: 20110921 Conference End: 20110924. Conference Publication: (var.pagings). 5 (1) (pp 141), 2011. Date of Publication: September 2011.		
26	Churyukanov MV, Alexeev VV, Kukushkin ML, Krupina NA and Yakhno NN. Chronic pain syndrome in multiple sclerosis. European Journal of Pain Supplements. Conference: 3rd International Congress on Neuropathic Pain Athens Greece. Conference Start: 20100527 Conference End: 20100530. Conference Publication: (var.pagings). 4 (1) (pp 101), 2010. Date of Publication: April 2010.	*Unobtainable - Conference Abstract only*	Emailed and awaiting response
27	D'Amico, D., L. La Mantia, et al. (2004). "Prevalence of primary headaches in people with multiple sclerosis." Cephalalgia 24(11): 980-984.	MS pain but biomedical	
28	Dane, J. R. (1996). "Hypnosis for pain and neuromuscular rehabilitation with multiple sclerosis: Case summary, literature review, and analysis of outcomes." International Journal of Clinical and Experimental Hypnosis 44(3): 208-231.	*Unobtainable*	
29	Damsbo AM. Trigeminal neuralgia treated by hypnosis: a case report. American Journal of Clinical Hypnosis. 17 (2) (pp 133-134), 1974. Date of Publication: 1974.	Non-empirical - Case Report	
30	De Santi L and Annunziata P. Symptomatic cranial neuralgias in multiple sclerosis: Clinical features and treatment. Clinical Neurology and Neurosurgery. 2012; 114: 101-7.	Biomedical	
31	Devins GM, Edworthy SM, Paul LC, et al. Restless sleep, illness intrusiveness, and depressive symptoms in 3 chronic illness conditions - rheumatoid-arthritis, end-stage renal-disease, and multiple-sclerosis. Journal of Psychosomatic Research. 1993; 37: 163-70.	Non-pain related	
32	Douglas, C., C. Windsor, et al. (2008). "Understanding chronic pain complicating disability: finding meaning through focus group methodology." Journal of Neuroscience Nursing 40(3): 158-168.	Qualitative Study	No mixed method data
33	Doulatabad SN, Nooreyan K, Doulatabad AN and Noubandegani ZM. The effects of pranayama, hatha and raja yoga on physical pain and the quality of life of women with multiple sclerosis. African Journal of Traditional Complementary and Alternative Medicines. 2013; 10: 49-52.	No psychological measures	
34	Ehde, D. M., T. L. Osborne, et al. (2005). "Chronic pain in persons with multiple sclerosis." Physical Medicine & Rehabilitation Clinics of North America 16(2): 503-512.	Not Empirical	
35	Ehde DM, Jensen MP, Engel JM, Turner JA, Hoffman AJ and Cardenas DD. Chronic pain secondary to disability: A review. Clinical Journal of Pain. 19 (1) (pp 3-17), 2003. Date of Publication: January/February 2003.	Review	
36	Elliott, D. G. (2007). "Migraine in multiple sclerosis." International Review of Neurobiology 79: 281-302.	MS pain but biomedical	
37	Ergun, U., G. Ozer, et al. (2009). "Headaches in the different phases of relapsing-remitting multiple sclerosis: a tendency for stabbing headaches during relapses." Neurologist 15(4): 212-216.	No pain measurements	
38	Feijoo De Freixo M, Jimenez Garcia M, Martinez Muerza F and Lunar Dominiguez A. Painful tonic seizures in multiple sclerosis. Clinical and electromyographic aspects. [Spanish]. Medicina	Biomedical	

	Clinica. 76 (10) (pp 454-456), 1981. Date of Publication: 1981.		
39	Foley PL, Vesterinen HM, Laird BJ, et al. Prevalence and natural history of pain in adults with multiple sclerosis: Systematic review and meta-analysis. Pain. 2013; 154: 632-42.	Biomedical review	
40	Forbes, A., A. While, et al. (2006). "Health problems and health-related quality of life in people with multiple sclerosis." Clinical Rehabilitation 20(1): 67-78.	Not a validated pain measurement	
41	Garinger, J. C. (2007). "Evaluating the effects of cognitive-behavioral group treatment for chronic pain management in individuals with multiple sclerosis." Dissertation Abstracts International: Section B: The Sciences and Engineering 68(4-B): 2648. (Grey Lit. Study)	Mediating psychological factors not explored	Methodological limitations (sample size was small and uncontrolled)
42	Garland EL and Howard MO. Mindfulness-oriented recovery enhancement reduces pain attentional bias in chronic pain patients. Psychotherapy and Psychosomatics. 82 (5) (pp 311-318), 2013. Date of Publication: August 2013.	**Not MS Sample**	
43	Gay MC, Vrignaud P, Garitte C and Meunier C. Predictors of depression in multiple sclerosis patients. Acta Neurologica Scandinavica. 2010; 121: 161-70.	Pain not measured in conjunction with psychological measures	
44	Grau-Lopez L, Sierra S, Martinez-Caceres E and Ramo-Tello C. Analysis of the pain in multiple sclerosis patients. [Spanish]. Neurologia. 26 (4) (pp 208-213), 2011. Date of Publication: May 2011.	Not Written in English	
45	Gelfand AA, Gelfand JM and Goadsby PJ. Migraine and multiple sclerosis: Epidemiology and approach to treatment. Multiple Sclerosis and Related Disorders. 2 (2) (pp 73-79), 2013. Date of Publication: April 2013.	Biomedical	
46	Ghaaliq Lalkhen A, Bedford JP and Dwyer AD. Pain associated with multiple sclerosis: epidemiology, classification and management. British Journal of Neuroscience Nursing. 2012; 8: 267-73.	Biomedical	
47	Hadjimichael, O., R. D. Kerns, et al. (2007). "Persistent pain and uncomfortable sensations in persons with multiple sclerosis." Pain 127(1-2): 35-41	Not a validated pain measurement	
48	Heckman-Stone, C. and C. Stone (2001). "Pain management techniques used by patients with multiple sclerosis." Journal of Pain 2(4): 205-208.	Not a validated pain measurement	
49	Higginson IJ, Hart S, Silber E, Burman R and Edmonds P. Symptom prevalence and severity in people severely affected by multiple sclerosis. Journal of Palliative Care. 22 (3) (pp 158-165), 2006. Date of Publication: Autumn 2006.	*Unobtainable - Abstract only*	
50	Hirsh AT, Bockow TB and Jensen MP. Catastrophizing, pain, and pain interference in individuals with disabilities. American journal of physical medicine & rehabilitation / Association of Academic Physiatrists. 90 (9) (pp 713-722), 2011. Date of Publication: Sep 2011.	Pain conditions effects not separated to show MS only	
51	Hirsh AT, Turner AP, Ehde DM, Haselkorn JK. Prevalence and impact of pain in multiple sclerosis: physical and psychologic contributors. Archives of Physical Medicine & Rehabilitation 2009;90(4):646-651.	Pain severity and interference only explored in relation to Quality of life measures, not modifiable psychosocial factors.	
52	Hnojcikova M, Vlckova E, Okacova I, et al. Evaluation of sensory and pain perception and mechanisms of central modulation of pain	Biomedical	Could not locate contact email

	perception in patients with multiple sclerosis (a pilot study). Journal of Neurology. 2012; 259: S167-S.		
53	Hobart	Duplication of Kalia and O'Connor	
54	Hoffman, K., A. Thompson, et al. (2004). "Anxiety, rather than depression, is the key to pain in MS." Multiple Sclerosis Journal 10: S149-S149.	*Unobtainable - Abstract available only*	No email address located
55	Hoffman, K., A. Thompson, et al. (2004). "Cognitive bias towards pain and MS; mediated by coping styles." Multiple Sclerosis Journal 10: S149-S149.	*Unobtainable - Abstract available only*	No email address located
56	Howarth, A. L. (2000). "Pain management for multiple sclerosis patients." Professional Nurse 16(1): 824-826.	*Unobtainable*	
57	Howarth AL and Freshwater D. Focus. Examining the benefits of aromatherapy massage as a pain management strategy for patients with multiple sclerosis. NT Research. 2004; 9: 120-8.	*Unobtainable - Abstract only*	
58	Hughes CM, Smyth S and Lowe-Strong AS. Reflexology for the treatment of pain in people with multiple sclerosis: A double-blind randomised sham-controlled clinical trial. Multiple Sclerosis. 15 (11) (pp 1329-1338), 2009. Date of Publication: 2009.	Pain not measured in conjunction with psychological measures	
59	Hughes GRV. Migraine, memory loss, and "multiple sclerosis". Neurological features of the antiphospholipid (Hughes') syndrome. Postgraduate Medical Journal. 79 (928) (pp 81-83), 2003. Date of Publication: 01 Feb 2003.	Biomedical review	
60	Improve treatment of multiple sclerosis by defining specific pain syndromes and analysing their relationship to the disease. Drugs & Therapy Perspectives. 2009; 25: 14-7.	*Unobtainable*	
61	Iskedjian M, Piwko C, Desjardins O, Bereza B, Jaszewski B and Einarson TR. Treatment of neuropathic pain in multiple sclerosis: A population based willingness-to-pay analysis. Value in Health. 2006; 9: A378-A.	No psychological measures	
62	Janssens, A. C., Van Doorn, P. A., De Boer, J. B., Kalkers, N. F., van der Meché, F. G., Passchier, J., & Hintzen, R. Q. (2003). A nxiety and depression influence the relation between disability status and quality of life in multiple sclerosis. *Multiple sclerosis*, *9*(4), 397-403.	Pain not examined directly in relation to psychological factors (anxiety and depression).	
63	Jensen, M. P., J. Barber, et al. (2009). "A comparison of self-hypnosis versus progressive muscle relaxation in patients with multiple sclerosis and chronic pain." International Journal of Clinical and Experimental Hypnosis 57(2): 198-221.	Mediating psychological factors not explored, no direct correlations or comparisons between pain vs. no pain groups	
64	Jensen, M. P., M. R. Moore, et al. (2011). "Psychosocial factors and adjustment to chronic pain in persons with physical disabilities: a systematic review." Archives of Physical Medicine & Rehabilitation 92(1): 146-160.	Systematic Review	
65	Jensen MP, Chodroff MJ and Dworkin RH. The impact of neuropathic pain on health-related quality of life - Review and implications. Neurology. 2007; 68: 1178-82.	Systematic Review	
66	Jensen MP, Ehde DM, Gertz KJ, et al. Effects of self-hypnosis training and cognitive restructuring on daily pain intensity and catastrophizing in individuals with multiple sclerosis and chronic pain. International Journal of Clinical and Experimental Hypnosis. 59 (1) (pp 45-63), 2011. Date of Publication: January 2011.	Mediating psychological factors not explored, no direct correlations or comparisons between pain vs. no pain groups	

67	Jensen MP, Hanley MA, Engel JM, et al. Hypnotic analgesia for chronic pain in persons with disabilities: A case series. International Journal of Clinical and Experimental Hypnosis. 2005; 53: 198-228.	Non – empirical - Case-Series	
68	Jensen MP. Pain in patients with disabilities: Introduction. Clinical Journal of Pain. 19 (1) (pp 1-2), 2003. Date of Publication: January/February 2003.	Non empirical - Commentary/Introduction	
69	Johnson K, Amtmann D, Cook K, et al. Course of depressive symptoms over time in multiple sclerosis. Multiple Sclerosis. Conference: 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS, 15th Annual Conference of Rehabilitation in MS, RIMS Gothenburg Sweden. Conference Start: 20101013 Conference End: 20101016. Conference Publication: (var.pagings). 16 (10 SUPPL. 1) (pp S220), 2010. Date of Publication: October 2010.	Conference Abstract not examining pain in conjunction with psychological factors	
70	Johnson K, Bamer A, Verrall A and McMullen K. Predicting unemployment in people ageing with multiple sclerosis. Multiple Sclerosis. Conference: 5th Joint Triennial Congress of the European and Americas Committees for Treatment and Research in Multiple Sclerosis Amsterdam Netherlands. Conference Start: 20111019 Conference End: 20111022. Conference Publication: (var.pagings). 17 (10 SUPPL. 1) (pp S486-S487), 2011. Date of Publication: October 2011.	*Unobtainable*	
71	Johnson K, McMullen K, Bamer A and Molton I. Prevalence of sexual satisfaction and impact of pain, fatigue, and other factors in people with multiple sclerosis. Multiple Sclerosis. Conference: 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS, 15th Annual Conference of Rehabilitation in MS, RIMS Gothenburg Sweden. Conference Start: 20101013 Conference End: 20101016. Conference Publication: (var.pagings). 16 (10 SUPPL. 1) (pp S20), 2010. Date of Publication: October 2010.	*Unobtainable*	
72	Julian LJ. Cognitive Functioning in Multiple Sclerosis. Neurologic Clinics. 29 (2) (pp 507-525), 2011. Date of Publication: May 2011.	No pain measurements	
73	Kenner M, Menon U and Elliott DG. Multiple sclerosis as a painful disease. Neurobiology of Multiple Sclerosis. 2007; 79: 303-21.	Unobtainable & Biomedical	
74	Kehler, M. D. and H. D. Hadjistavropoulos (2009). "Is health anxiety a significant problem for individuals with multiple sclerosis?" Journal of Behavioral Medicine 32(2): 150-161.	No pain measurements	
75	Kerns, R. (2000) Psychosocial Aspects of Pain. Int J MS Care [Serial on-line]	Not Empirical	
76	Kerns, R. D., M. Kassirer, et al. (2002). "Pain in multiple sclerosis: a biopsychosocial perspective." Journal of Rehabilitation Research & Development 39(2): 225-232.	Not Empirical	
77	Khan F, Amatya B, Kesselring, J. (2013) Longitudinal 7-year follow-up of chronic pain in persons with multiple sclerosis. J Neurology. 260: 2005-2015	No modifiable psychological measures examined only QoL	
78	Kister, I., A. B. Caminero, et al. (2010). "Migraine is comorbid with multiple sclerosis and associated with a more symptomatic MS course." Journal of Headache & Pain 11(5): 417-425.	*Unobtainable - Abstract/summary available only*	
79	Kister I, Caminero AB, Herbert J and Lipton RB. Tension-type Headache and Migraine in Multiple	Biomedical Review	

	Sclerosis. Current Pain and Headache Reports. 2010; 14: 441-8.		
80	Knafo R, Haythornthwaite JA, Heinberg L, Wigley FM and Thombs BD. The association of body image dissatisfaction and pain with reduced sexual function in women with systemic sclerosis. Rheumatology. 2011; 50: 1125-30.	**Not MS**	
81	Kratz AL, Hirsh AT, Ehde DM and Jensen MP. Acceptance of pain in neurological disorders: Associations with functioning and psychosocial well-being. Rehabilitation Psychology. 58 (1) (pp 1-9), 2013.	The study investigated mixed chronic pain populations not looking at MS alone, and did not assess the direct relationship between psychosocial factors and pain interference.	
82	Kratz AL, Davis MC and Zautra AJ. Attachment Predicts Daily Catastrophizing and Social Coping in Women With Pain. Health Psychology. 2012; 31: 278-85.	**Not MS**	
83	Lauckaite K, Mickeviciene D, Petrikonis K and Rastenyte D. Clinical exacerbations of multiple sclerosis and the features of pain associated with MS. Multiple Sclerosis. Conference: 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS, 15th Annual Conference of Rehabilitation in MS, RIMS Gothenburg Sweden. Conference Start: 20101013 Conference End: 20101016. Conference Publication: (var.pagings). 16 (10 SUPPL. 1) (pp S62-S63), 2010. Date of Publication: October 2010.	Review	
84	Malciene L, Mickeviciene D, Petrikonis K, Sciupokas A, Straukiene A and Lauckaite K. A multidimensional assessment of multiple sclerosis related-pain: A prospective study. Multiple Sclerosis. Conference: 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis Dusseldorf Germany. Conference Start: 20090909 Conference End: 20090912. Conference Publication: (var.pagings). 15 (9 Suppl. S) (pp S49-S50), 2009. Date of Publication: September 2009.	*Unobtainable*	
85	Maloni HW. Pain in multiple sclerosis: an overview of its nature and management. Journal of Neuroscience Nursing. 2000; 32: 139-44, 52.	Non-empirical	
86	Marchettini P, Formaglio F and Lacerenza M. Pain as heralding symptom in multiple sclerosis. Neurological Sciences. 2006; 27: S294-S6.	Case studies	
87	Marjanovic, I. V., J. R. Kostic, et al. (2007). "Pain influence on depression and anxiety in patients with multiple sclerosis." European Journal of Neurology 14: 283-283.	*Unobtainable - Abstract/summary available only*	Not enough information for quality assessment and data extraction (Authors emailed). No email address located.
88	Mastaglia FL. The relationship between muscle pain and fatigue. Neuromuscular Disorders. 22 (SUPPL. 3) (pp S178-S180), 2012. Date of Publication: 01 Dec 2012.	**Not MS**	
89	Maurer M and Rieckmann P. Pain in multiple sclerosis. Nervenheilkunde. 1999; 18: 517-21.	Review	
90	Predictors and health impact of exercise capacity in multiple sclerosis http://digitool.Library.McGill.CA:80/R/?func=dbin-jump-full&object_id=66825 Author(s): Nancy Mayo (Supervisor); Kuspinar, Ayse Publication: McGill University 2009Dissertation: Thesis / Dissertation ETD Document: English : Internet Resource Libraries Worldwide: 1 (WorldCatDissertations)	No psychological measures	World cat

91	McMullen K, Bamer A, Bombardier C, Ehde D and Bowen J. Motivational interviewing to increase exercise in multiple sclerosis. Multiple Sclerosis. Conference: 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis Dusseldorf Germany. Conference Start: 20090909 Conference End: 20090912. Conference Publication: (var.pagings). 15 (9 Suppl. S) (pp S256-S257), 2009. Date of Publication: September 2009.	*Unobtainable*	
92	Messmer Uccelli M, Specchia C, Battaglia MA and Miller DM. Factors that influence the employment status of people with multiple sclerosis: A multi-national study. Journal of Neurology. 256 (12) (pp 1989-1996), 2009. Date of Publication: December 2009.	No psychological factors in conjunction with pain	
9394	Milette K, Razykov I, Pope J, et al. Clinical correlates of sleep problems in systemic sclerosis: the prominent role of pain. Rheumatology. 2011; 50: 921-5..	**Not MS**	
94	Mohrke J, Kropp P, Zettl UK. Headaches in Multiple Sclerosis Patients Might Imply an Inflammatorial Process: PLoS ONE. 8 (8) , 2013. Article Number: e69570. Date of Publication: 05 Aug 2013	Though headache was looked at comparing BDI with no difference in proportions using Chi2, severity or interference of headache was not used. Instead IHS classification was used. Also a BDI cut-off was not stated.	
95	Molton I, Jensen M, Amtmann D, Johnson K, Ehde D and Kraft G. Activity restriction, pain and mood across the lifespan in adults with multiple sclerosis or spinal cord injury. Multiple Sclerosis. Conference: 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis Dusseldorf Germany. Conference Start: 20090909 Conference End: 20090912. Conference Publication: (var.pagings). 15 (9 Suppl. S) (pp S266), 2009. Date of Publication: September 2009.	*Unobtainable*	
96	Molton I, Jensen MP, Ehde DM, Carter GT, Kraft G and Cardenas DD. Coping with chronic pain among younger, middle-aged, and older adults living with neurological injury and disease. Journal of Aging and Health. 20 (8) (pp 972-996), 2008. Date of Publication: December 2008.	The study investigated mixed chronic pain populations not looking at MS alone, and did not assess the direct relationship between psychosocial factors and pain severity and interference.	
97	Moore, P., Harding, K. E., Clarkson, H., Pickersgill, T. P., Wardle, M., & Robertson, N. P. (2013). Demographic and clinical factors associated with changes in employment in multiple sclerosis. *Multiple Sclerosis Journal*.	No psychological factors in conjunction with pain	
98	Morin C, Bushnell M, Luskin MB and Craig A. Disruption of thermal perception in a multiple sclerosis patient with central pain. The Clinical Journal of Pain. 2002; 18: 191-5.	Case Study	
99	Motl, R. W. and E. McAuley (2009). "Symptom cluster as a predictor of physical activity in multiple sclerosis: Preliminary evidence." Journal of Pain and Symptom Management 38(2): 270-280.	Pain embedded with other symptoms (unclear of unique relationship with psychological factors)	
100	Motl, R. W., Y. Suh, et al. (2010). "Symptom cluster and quality of life in multiple sclerosis." Journal of Pain and Symptom Management 39(6): 1025-1032.	Pain embedded with other symptoms	

101	Motl, R. W., M. Weikert, et al. (2010). "Symptom cluster and physical activity in relapsing-remitting multiple sclerosis." Research in Nursing & Health 33(5): 398-412.	Pain embedded with other symptoms	
102	Motl RW, McAuley E and Sandroff BM. Longitudinal change in physical activity and its correlates in relapsing-remitting multiple sclerosis. Physical therapy. 93 (8) (pp 1037-1048), 2013. Date of Publication: Aug 2013.	*Unobtainable*	
103	Motl RW, McAuley E, Snook EM and Gliottoni RC. Physical activity and quality of life in multiple sclerosis: Intermediary roles of disability, fatigue, mood, pain, self-efficacy and social support. Psychology, Health and Medicine. 14 (1) (pp 111-124), 2009. Date of Publication: January 2009.	No psychological factors in conjunction with pain	
104	Motl RW, McAuley E and Suh Y. Validity, invariance and responsiveness of a self-report measure of functional limitations and disability in multiple sclerosis. Disability and rehabilitation. 32 (15) (pp 1260-1271), 2010. Date of Publication: 2010.	No psychological factors in conjunction with pain	
105	Newland, P. (2008). "Pain in women with relapsing-remitting multiple sclerosis and in healthy women: a comparative study." Journal of Neuroscience Nursing 40(5): 262-268.	No psychological variables	
106	Newland PK, Naismith RT and Ullione M. The impact of pain and other symptoms on quality of life in women with relapsing-remitting multiple sclerosis. The Journal of neuroscience nursing: journal of the American Association of Neuroscience Nurses. 41 (6) (pp 322-328), 2009. Date of Publication: Dec 2009.	Relationships between psychological factors and MS pain not explored	
107	Newland PK, Thomas FP, Riley M, Flick LH and Fearing A. The Use of Focus Groups to Characterize Symptoms in Persons With Multiple Sclerosis. Journal of Neuroscience Nursing. 2012; 44: 351-7.	Qualitative study	
108	Ni WJ, Hadjimichael O, Vollmer TL and Rizzo M. Pain syndromes in MS: Severity, impact on quality of life, and treatment patterns. Neurology. 2001; 56: A98-A.	Brief report / No psychological factors in conjunction with pain	
109	Nick ST, Robertsa C, Billiodeaux S, et al. Multiple sclerosis and pain. Neurological Research. 34 (9) (pp 829-841), 2012. Date of Publication: 2012.	Biomedical review	
110	Niino M. Painful symptoms and quality of life in multiple sclerosis. Neurology Asia. 2008; 13: 185-7.	Not empirical	
111	Noonan V, Amtmann D, Brockway JA, Bamer A, Johnson K and Cook K. Self efficacy scale for persons with SCI and multiple sclerosis. Journal of Spinal Cord Medicine. Conference: 36th Annual Scientific Meeting of the American Spinal Injury Association Nashville, TN United States. Conference Start: 20100526 Conference End: 20100528. Conference Publication: (var.pagings). 33 (2) (pp 173), 2010. Date of Publication: 2010.	*Unobtainable*	
112	Nurmikko T. Pain mechanisms in multiple sclerosis. Pain. 2012; 153: 1991-2.	Commentary / Not empirical	
113	Nurmikko TJ, Gupta S and Maclver K. Multiple sclerosis-related central pain disorders. Current Pain and Headache Reports. 14 (3) (pp 189-195), 2010. Date of Publication: June 2010.	Commentary / Not empirical	
114	O'Connor, A. B., S. R. Schwid, et al. (2008). "Pain associated with multiple sclerosis: Systematic review and proposed classification." Pain 137(1): 96-111.	Not empirical	
115	Orejas Monfort E, Castrillo Amores MA and	Conference abstract /	

	Lopez Jimenez A. Pain in multiple sclerosis. Neurorehabilitation and Neural Repair. Conference: 1st European NeuroRehabilitation Congress, ENRC 2011 Merano Italy. Conference Start: 20111020 Conference End: 20111022. Conference Publication: (var.pagings). 26 (4) (pp 431-432), 2012. Date of Publication: May 2012.	Biomedical	
116	Oreste R, Roberto C, Emanuela G, et al. Efficacy and neurophysiological evalutation in multiple sclerosis patients treated with percutaneous tibial nerve stimulation. Neurourology and Urodynamics. Conference: 36th Annual Congress of the Italian Urodynamic Society Florence Italy. Conference Start: 20120524 Conference End: 20120526. Conference Publication: (var.pagings). 31 (pp S40-S41), 2012. Date of Publication: June 2012.	**Not MS**	
117	Osborne TL, Raichle KA, Jensen MP, Ehde DM and Kraft G. The Reliability and Validity of Pain Interference Measures in Persons with Multiple Sclerosis. Journal of Pain and Symptom Management. 32 (3) (pp 217-229), 2006. Date of Publication: September 2006.	Factor analyses but no clear correlations of subgroups	
118	Osterberg A and Boivie J. Central pain in multiple sclerosis - Sensory abnormalities. European Journal of Pain. 14 (1) (pp 104-110), 2010. Date of Publication: January 2010.	Biomedical	
119	Osterberg A, Boivie J and Thuomas KA. Central pain in multiple sclerosis - prevalence and clinical characteristics. European Journal of Pain. 2005; 9: 531-42.	Biomedical	
120	Ozgocmen S, Kaya A, Gulkesen A, Bulut S and Ardicoglu O. Comparison of pain threshold, health and functional status of females with fibromyalgia and multiple sclerosis: A pilot study. International Journal of Psychiatry in Clinical Practice. 10 (3) (pp 160-165), 2006. Date of Publication: 01 Sep 2006.	Biomedical	
121	Paddam A, Barnes D and Langdon D. Why are multiple sclerosis patients angry? A preliminary quantitative study of factors associated with anger in multiple sclerosis. Multiple Sclerosis. Conference: 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis Dusseldorf Germany. Conference Start: 20090909 Conference End: 20090912. Conference Publication: (var.pagings). 15 (9 Suppl. S) (pp S228), 2009. Date of Publication: September 2009.	Conference abstract only – Grey thesis found but no pain measures in conjunction with psychological measures.	
122	Pagoto S. Psychological co-morbidities of physical illness: A behavioral medicine perspective. 2011; 466.	Book chapter of mixed pain conditions	
123	Pakenham, K. and M. Fleming (2011). "Relations between acceptance of multiple sclerosis and positive and negative adjustments." Psychology & Health 26(10): 1292-1309.	Relationships between psychological factors and MS pain not explored	Relevant psychological factor but is not set against MS pain
124	Pakenham KI and Samios C. Couples coping with multiple sclerosis: a dyadic perspective on the roles of mindfulness and acceptance. Journal of Behavioral Medicine. 2013; 36: 389-400.	No pain measures	
125	Pakpoor J, Handel AE, Giovannoni G, Dobson R and Ramagopalan SV. Meta-Analysis of the Relationship between Multiple Sclerosis and Migraine. PLoS ONE. 2012; 7.	Biomedical review	
126	Pau D, Al Zubidi N, Yalamanchili S, Plant GT and Lee AG. Optic neuritis. Eye. 25 (7) (pp 833-842), 2011. Date of Publication: July 2011.	Biomedical review	
127	Paulig M. Pain and multiple sclerosis. Nervenheilkunde. 2009; 28: 875-8.	*Unobtainable*	

128	Phillips LJ and Stuifbergen AK. The relevance of depressive symptoms and social support to disability in women with multiple sclerosis or fibromyalgia. International journal of rehabilitation research. Internationale Zeitschrift fur Rehabilitationsforschung. Revue internationale de recherches de readaptation. 33 (2) (pp 142-150), 2010. Date of Publication: Jun 2010.	No pain measures	
129	Perkins, F. M., R. T. Moxley, III, et al. (1999). "Pain in multiple sclerosis and the muscular dystrophies." Block, Andrew R [Ed]: 349-370.	Book chapter	
130	Phillips LJ and Stuifbergen AK. Structural equation modeling of disability in women with fibromyalgia or multiple sclerosis. Western Journal of Nursing Research. 31 (1) (pp 89-109), 2009. Date of Publication: February 2009.	No pain measures	
131	Piwko C, Desjardins OB, Bereza BG, et al. Pain due to multiple sclerosis: Analysis of the prevalence and economic burden in Canada. Pain Research & Management. 2007; 12: 259-65.	No pain or psychological measures	
132	Pollmann, W. and W. Feneberg (2008). "Current management of pain associated with multiple sclerosis." CNS Drugs 22(4): 291-324.	Systematic Review	
133	Pollmann W and Feneberg W. Pain in multiple sclerosis - modern resources of neurological rehabilitation. Nervenheilkunde. 1999; 18: 526-31.	*Unobtainable*	
134	Pollmann W, Feneberg W, Steinbrecher A, Haupts MR and Henze T. Therapy of pain syndromes in multiple sclerosis - An overview with evidence-based recommendations. Fortschritte Der Neurologie Psychiatrie. 2005; 73: 268-85.	Not written in English	
135	Qian P, Cross A and Naismith R. Pain in neuromyelitis optica is more common, disabling, and refractory compared to MS. Neurology. Conference: 64th American Academy of Neurology Annual Meeting New Orleans, LA United States. Conference Start: 20120421 Conference End: 20120428. Conference Publication: (var.pagings). 78 (1 Meeting Abstract) , 2012. Date of Publication: 22 Apr 2012.	*Conference abstract - Unobtainable*	
136	Pugliatti, M., T. Riise, et al. (2008). "Self-perceived physical functioning and health status among fully ambulatory multiple sclerosis patients." Journal of Neurology 255(2): 157-162.	No pain measurements	
137	Putzki, N. and Z. Katsarava (2010). "Headache in Multiple Sclerosis." Current Pain and Headache Reports 14(4): 316-320.	MS pain but biomedical	
138	Quality of life perception in MS patients influenced by more than disability. Pharmacy Times. 79 (2), 2013. Date of Publication: February 2013.	*Unobtainable*	
139	Rae-Grant AD. Unusual symptoms and syndromes in multiple sclerosis. CONTINUUM: Lifelong Learning in Neurology. 2013; 19: 992-1006.	Biomedical Review	
140	Rae-Grant AD, Eckert NJ, Bartz S and Reed JF. Sensory symptoms of multiple sclerosis: A hidden reservoir of morbidity. Multiple Sclerosis. 5 (3) (pp 179-183), 1999. Date of Publication: June 1999.	Biomedical	
141	Rae-Grant AD, Turner AP, Sloan A, Miller D, Hunziker J and Haselkorn JK. Self-management in neurological disorders: Systematic review of the literature and potential interventions in	Review	

	multiple sclerosis care. Journal of Rehabilitation Research and Development. 48 (9) (pp 1087-1100), 2011. Date of Publication: 2011.		
142	Rohrmann S, Hopf M, Hennig J and Netter P. Psychobiological effects of autogenic training and progressive muscle relaxation in health subjects and patients with back pain or multiple sclerosis. Zeitschrift Fur Klinische Psychologie Psychiatrie Und Psychotherapie. 2001; 49: 373-87.	*Unobtainable*	
143	Sabanagic-Hajric, S., A. Alajbegovic, et al. (2010). "Influence of pain and sphincterial disorders on quality of life in multiple sclerosis patients." European Journal of Neurology 17: 234-234.	MS pain but biomedical	
144	Sabanagic-Hajric S, Subasic N and Alajbegovic A. Predictive factors of physical component of quality of life in multiple sclerosis patients. Journal of the Neurological Sciences. Conference: 21st World Congress of Neurology Vienna Austria. Conference Start: 20130921 Conference End: 20130926. Conference Publication: (var.pagings). 333 (pp e388-e389), 2013. Date of Publication: 15 Oct 2013.	*Unobtainable - Conference abstract related to QoL*	
145	Sahai-Srivastava, S., S. L. Wang, et al. (2012). "Impact of Depression and Racial Factors on Primary Headache in Multiple Sclerosis." Headache 52(5): 890-890.	*Unobtainable - Abstract available only*	Author emailed a request (no response)
146	Salci Y, Aydotan S, Fil A, et al. Pain in turkish patients with multiple sclerosis: Preliminary results. Neurorehabilitation and Neural Repair. Conference: 7th World Congress for NeuroRehabilitation, WCNR 2012 Melbourne, VIC Australia. Conference Start: 20120516 Conference End: 20120519. Conference Publication: (var.pagings). 26 (6) (pp 661), 2012. Date of Publication: July-August 2012.	Conference abstract only - No psychological factors in conjunction with pain	
147	Schmidt R, Krauss B and Weiss M. Psychotherapeutic interventions in the treatment of comorbid psychological disorders in multiple sclerosis. [German]. Neurologie und Rehabilitation. 12 (4) (pp 214-223), 2006. Date of Publication: October 2006.	Not empirical	
148	Seixas D, Palace J, Miller K, et al. A clinical and imaging protocol for the detailed evaluation of chronic neuropathic pain in multiple sclerosis. European Journal of Pain. Conference: 6th Congress of the European Federation of IASP Chapters: Pain in Europe 6th, EFIC Lisbon Portugal. Conference Start: 20090909 Conference End: 20090912. Conference Publication: (var.pagings). 13 (pp S71), 2009. Date of Publication: September 2009.	Biomedical conference abstract	
149	Seixas, D., Sá, M. J., Galhardo, V., Guimarães, J., & Lima, D. (2011). Pain in Portuguese patients with multiple sclerosis. *Frontiers in neurology*, *2*.	No psychological measures	
150	Seixas D, Palace J, Jbabdi S, et al. The thalamus and neuropathic pain in multiple sclerosis. Journal of Neurology, Neurosurgery and Psychiatry. Conference: ABN joint Annual Meeting 2009 with the Spanish Society of Neurology Liverpool United Kingdom. Conference Start: 20090622 Conference End: 20090626. Conference Publication: (var.pagings). 80 (11) , 2009. Date of Publication: November 2009.	Biomedical conference abstract	
151	Seixas D, Palace J, Jbabdi S, et al. Chronic neuropathic pain in multiple sclerosis: Clinical and imaging findings, with a special focus on the thalamus. European Journal of Pain. Conference: 6th Congress of the European Federation of IASP	Biomedical conference abstract	

	Chapters: Pain in Europe 6th, EFIC Lisbon Portugal. Conference Start: 20090909 Conference End: 20090912. Conference Publication: (var.pagings). 13 (pp S144), 2009. Date of Publication: September 2009.		
152	Shutty MS, Jr., DeGood DE and Tuttle DH. Chronic pain patients' beliefs about their pain and treatment outcomes. Archives of Physical Medicine & Rehabilitation. 1990; 71: 128-32.	*Unobtainable*	
153	Seixas D, Sa MJ, Galhardo V, Guimaraes J and Lima D. Pain in portuguese patients with multiple sclerosis. Frontiers in neurology [electronic resource]. 2011; 2: 20.	No psychological measures used	
154	Smith RM, Adeney-Steel M, Fulcher G and Longley WA. Symptom change with exercise is a temporary phenomenon for people with multiple sclerosis. Archives of Physical Medicine and Rehabilitation. 2006; 87: 723-7.	No pain or psychological measures	
155	Smitherman TA and Ward TN. Psychosocial Factors of Relevance to Sex and Gender Studies in Headache. Headache: The Journal of Head & Face Pain. 2011; 51: 923-31.	Review	
156	Solaro C, Cella M, Pedemonte E, et al. Prevalence of pain in multiple sclerosis: A multicenter Italian study. Journal of the Peripheral Nervous System. Conference: Meeting of the Associazione Italiana Sistema Nervoso Periferico and Gruppo Neuroscienze e Dolore della Societa Italiana di Neurologia 2012 Pisa Italy. Conference Start: 20120412 Conference End: 20120414. Conference Publication: (var.pagings). 17 (pp S51-S52), 2012. Date of Publication: April 2012.	*Unobtainable - Conference abstract only*	Contacted and awaiting response
157	Solaro C, Trabucco E and Uccelli MM. Pain and Multiple Sclerosis: Pathophysiology and Treatment. Current Neurology and Neuroscience Reports. 2013; 13.	Biomedical review	
158	Sorgun MH, Yucesan C and Genc Y. Headache in multiple sclerosis. Turkish Journal of Medical Sciences. 2013; 43: 1042-9.	Relationships between psychological factors and MS pain not explored	
159	Stenager, E., L. Knudsen, et al. (1991). "Acute and chronic pain syndromes in multiple sclerosis." Acta Neurologica Scandinavica 84(3): 197-200.	Not a validated pain measurement	
160	Stenager EN, Koch-Henriksen N and Stenager E. Risk factors for suicide in multiple sclerosis. Psychotherapy & Psychosomatics. 1996; 65: 86-90.	No pain measures	
161	Stenager EN, Stenager E and Jensen K. Attempted-suicide, depression and physical diseases - a 1-year follow-up-study. Psychotherapy and Psychosomatics. 1994; 61: 65-73.	No VAS or NRS pain measures and pain or no pain groups not identified	
162	Stuijbergen, A. K., H. Becker, et al. (2003). "A randomized clinical trial of a wellness intervention for women with multiple sclerosis." Archives of Physical Medicine and Rehabilitation 84(4): 467-476.	No pain measurements	
163	Sullivan MJL, Weinshenker B, Mikail S and Bishop SR. Screening for major depression in the early stages of multiple-sclerosis. Canadian Journal of Neurological Sciences. 1995; 22: 228-31.	No pain measures	
164	Sullivan MJ, Weinshenker B, Mikail S and Edgley K. Depression before and after diagnosis of multiple sclerosis. Multiple Sclerosis. 1995; 1: 104-8.	No standard depression or pain measures stated (instead 'history of depression' and 'pain' in interviewing)	
165	Sullivan S, Ehde D, Turner J and Dillworth T. Acceptance, catastrophizing, and depressive	*Unobtainable - Conference abstract*	Author contacted no response

	symptoms in persons with disability-related chronic pain. Journal of Pain. Conference: 31st Annual Scientific Meeting of the American Pain Society Honolulu, HI United States. Conference Start: 20120516 Conference End: 20120519. Conference Publication: (var.pagings). 13 (4 SUPPL. 1) (pp S96), 2012. Date of Publication: April 2012.	*only*	
166	Sullivan MJL, Mikail S and Weinshenker B. Coping with a diagnosis of multiple sclerosis. Canadian Journal of Behavioural Science-Revue Canadienne Des Sciences Du Comportement. 1997; 29: 249-56.	Relationships between psychological factors and MS pain not explored	
167	Tavee J, Rensel M, Planchon SP and Stone L. Effects of Meditation on Pain and Quality of Life in Multiple Sclerosis and Polyneuropathy: A Controlled Study. Neurology. 2010; 74: A160-A.	*Conference abstract - Unobtainable*	
168	Tavee J and Stone L. Heaing the mind: Mediation and multiple sclerosis. Neurology. 2010; 75: 1130-1.	*Unobtainable*	
169	Taylor HB. Pain and women with spinal cord injury, multiple sclerosis, joint connective tissue disorders and other physical disabilities. Archives of Physical Medicine and Rehabilitation. Conference: 2012 American Congress of Rehabilitation Medicine (ACRM)-American Society of Neurorehabilitation (ASNR) Annual Conference Vancouver, BC Canada. Conference Start: 20121009 Conference End: 20121013. Conference Publication: (var.pagings). 93 (10) (pp E57), 2012. Date of Publication: October 2012.	Conference abstract – poster sent by author when emailed but an amalgam on neurological conditions.	
170	Teng SY. Assessing Cognitive Impairment in Multiple Sclerosis: Effect of Gender, Mood and Time. Faculty of Medicine, McGill University, Montreal, Quebec, Canada. 2009.	Looked at neurocognitive factors not pertaining to models outlined	
171	Thomas, P. W., S. Thomas, et al. (2006). "Psychological interventions for multiple sclerosis." Cochrane Database of Systematic Reviews (1): CD004431.	Not Empirical	
172	Thombs BD, Hudson M, Taillefer SS, Baron M and Canadian Scleroderma Res G. Prevalence and clinical correlates of symptoms of depression in patients with systemic sclerosis. Arthritis & Rheumatism-Arthritis Care & Research. 2008; 59: 504-9.	**Not MS**	
173	Tree H, Lynch S and Denney D. Prevalence and correlates of MS-related pain. Multiple Sclerosis. Conference: 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis Dusseldorf Germany. Conference Start: 20090909 Conference End: 20090912. Conference Publication: (var.pagings). 15 (9 Suppl. S) (pp S50), 2009. Date of Publication: September 2009.	*Unobtainable*	Could not locate contact details
174	Tree HA. Multiple sclerosis severity, pain intensity, and psychosocial factors: Associations with perceived social support, hope, optimism, depression, and fatigue. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2010; 70: 4499.	*Unobtainable*	Could not locate contact details
175	Turpin KVL, Janzen W, Warren SA and Warren KG. Predictors of unmet needs for mobility, agility and pain assistive devices among Canadians with multiple sclerosis. Multiple Sclerosis. Conference: 5th Joint Triennial Congress of the European and Americas Committees for Treatment and Research in Multiple Sclerosis Amsterdam Netherlands.	*Unobtainable*	

	Conference Start: 20111019 Conference End: 20111022. Conference Publication: (var.pagings). 17 (10 SUPPL. 1) (pp S250), 2011. Date of Publication: October 2011.		
176	Vacca G, Marano E, Morra VB, et al. Multiple sclerosis and headache co-morbidity. A case-control study. Neurological Sciences. 2007; 28: 133-5.	No psychological factors	
177	Velazquez A, Iniguez C, Santos S, Bellosta E and Garcia C. Trigeminal neuralgia and multiple sclerosis: Quality of life, headache impairment and anxiety-depressive symptoms. Journal of the Neurological Sciences. Conference: 21st World Congress of Neurology Vienna Austria. Conference Start: 20130921 Conference End: 20130926. Conference Publication: (var.pagings). 333 (pp e401-e402), 2013. Date of Publication: 15 Oct 2013.	*Unobtainable - Conference abstract showing no differences in depression or anxiety*	Could not locate contact details
178	Villani, V., L. Prosperini, et al. (2011). "Quality of life of multiple sclerosis patients with comorbid migraine." Neurological Sciences 32(Suppl 1): S149-S151.	No pain measurements	
179	Voiticovschi-Iosob C, Moldovanu I and Concescu D. The impact of chronic pain on the quality of life of patients with multiple sclerosis. European Journal of Neurology. 2012; 19: 634-.	Conference abstract no psychological measures	
180	Wang SL, Amezcua L and Sahai-Srivastava S. Headache impact and its correlates in multiple sclerosis. Headache. Conference: 54th Annual Scientific Meeting of the American Headache Society Los Angeles, CA United States. Conference Start: 20120621 Conference End: 20120624. Conference Publication: (var.pagings). 52 (5) (pp 883), 2012. Date of Publication: May 2012.	*Unobtainable - Conference abstract*	Could not locate contact details
181	Warnell, P. (1991). "The pain experience of a multiple sclerosis population: a descriptive study." AXON 13(1): 26-28.	Relationships between psychological factors and MS pain not explored	
182	Predictors of help-seeking behavior in adults with multiple sclerosis http://hdl.handle.net/1773/20633 Author: Weir, Virginia.; Trivedi, Ranak, Publication: 2012Dissertation: Thesis (M.P.H.)--University of Washington, 2012. Document: English : Internet Resource :	No pain measures	World cat
183	Yorkston, K. M., K. L. Johnson, et al. (2005). "Taking part in life: enhancing participation in multiple sclerosis." Physical Medicine & Rehabilitation Clinics of North America 16(2): 583-594.	Qualitative Study	
184	Yorkston KM, Johnson K, Boesflug E, Skala J and Amtmann D. Communicating about the experience of pain and fatigue in disability. Quality of Life Research. 2010; 19: 243-51.	Qualitative Study	
185	Yorkston KM, Kuehn CM, Johnson KL, Ehde DM, Jensen MP and Amtmann D. Measuring participation in people living with multiple sclerosis: A comparison of self-reported frequency, importance and self-efficacy. Disability and Rehabilitation. 30 (2) (pp 88-97), 2008. Date of Publication: 2008.	Relationships between psychological factors and MS pain not explored	

Manual search			
Of *k*=9, 8 were excluded (references listed below)			
No.	**Study Reference**	**Exclusion Basis**	**Comments**
1.	Connolly G., et al. (2011) Pain in multiple sclerosis an epidemiological study. MS frontiers programme 2011 Identified by fourth author at a conference.	*Unobtainable - Conference abstract only*	No email address located
2.	Gilmore R, Strong J. Pain and Multiple Sclerosis. British Journal of Occupational Therapy 1998;61 (4):169-172. Identified by 2nd author.	Pain severity and interference only explored in relation to Quality of life measures, not modifiable psychosocial factors.	
3.	Social Support, Depression, and Physical Disability: Age and Diagnostic Group Effects Mark P. Jensen, PhD1; Amanda E. Smith, BS1; Charles H. Bombardier, PhD1; Kathryn M. Yorkston, PhD1; Jordi Miró, PhD1; Ivan R. Molton, PhD2 Provided by the Jensen	No psychological measures in conjunction with pain measures	
4.	Linl, C. P., Kupperl, A. E., Gammaitonil, A. R., Galerl, B. S., & Jensenl, M. P. (2011). Frequency of chronic pain descriptors: Implications for assessment of pain quality. European Journal of Pain, 15(6), 628-633.	No pain measures	
5.	Macleod, L. and G. Macleod (1998). "Control cognitions and psychological disturbance in people with contrasting physically disabling conditions." Disability and Rehabilitation: An International, Multidisciplinary Journal 20(12): 448-456. Identified by 2nd author.	No pain measurements	
6.	Mills, N. and & Allen, J.(2000) Mindfulness of movement as a coping strategy in multiple sclerosis: a pilot study. General Hospital Psychiatry 22, 425–431 Identified by third author.	Not enough info about the measures used and their validity	
7.	Rosenberg, D.E., Bombardier, C.H., Artherholt, S.B., Jensen, M.P., & Motl, R.W. (in press). "Self-reported depression and physical activity in adults with mobility impairments". Archives of Physical Medicine and Rehabilitation. (Manual search Grey Literature paper identified by Professor Mark Jensen, UW).	The study investigated mixed chronic pain populations not looking at MS alone. Nor did it use any pain severity or interference measure	
8.	Sheppard, S. C., Forsyth, J. P., Hickling, E. J., & Bianchi, J. (2010). A novel application of acceptance and commitment therapy for psychosocial problems associated with multiple sclerosis: Results from a half-day workshop intervention. International Journal of MS Care, 12(4), 200-206.	Mediating psychological factors not explored, no direct correlations or comparisons between pain vs. no pain groups	

Supplementary Materials: Appendix C Quality Assessment Tool

(All Items scores as 0 = not present or 1 = present)
Scoring 0-15: ≤8 (53%) Poor; 9-12 (≥60-≤80%) Medium; 13-15 (≥86.6%) Good.

	Item Definition
Rationale- aims	**1:** Positive if the objective of the study was sufficiently described (question or hypothesis with either direction) and/or based of a theoretical model.
Demographic variables	**2**: Positive if information was reported on participant's gender, age, disease type/course, disease severity, time since diagnosis, current MS status (*at least 3 of these*)
Suitability of the design to answering the research question	**3:** Positive if appropriate research design was used, e.g. positive if control group was used when comparing psychopathology to the healthy population, if cross sectional design was used to find associations among the variables (not suggest causality or predictors), or qualitative methods were used to investigate in depth experiences of adults. **4:** Positive if control group was equivalent in age, sex and socioeconomic status (comparative studies)
The Sample	**5:** Positive if the source of the subjects studied is stated **6:** Positive if response/participation rate relative to non-participation was stated (how many questionnaires the researcher got back) **7:** Positive if the sample size was justified in relation to a power calculation and/or the number of independent variables utilised (a recognised rule of thumb is 10 times the number of IVs within a regression analysis: including control and psychological factors).
Statistical analysis	**8:** Positive if appropriate statistical methods of analysis were used for the data (specific to the context of the studies aims) **9.** Positive if an appropriate statistical adjustment was performed on factored into the design (confounders) **10.** Positive if the authors stated if normality distributions were met, and if not, whether data transformation was conducted prior to analysis (if required).
Presentation of the analysis	**11:** Positive if the graphs and tables were easy to understand, e.g. presenting a table for regression analyses including R^2 values and β weights
	12: Positive if confidence intervals or p values were given for the main results
Measures used	**13:** Positive if all the questionnaires used were standardized, defined as questionnaires that had been validated and published or psychometric properties of new measures were presented
Conclusions	**14:** Positive if the conclusions were justified based on the research findings
Limitations	**15:** Positive if key limitations were mentioned

Supplementary Materials: Appendix D Characteristics of Included Studies

Study Characteristics	Number (%)
Sample Recruitment Sources:	
MS Community & University Settings	14 (45%)
Inpatient, outpatient & Rehabilitation Centres	17 (55%)
Counties:	
USA	16
UK	4
Australia	4
Canada	1
France	2
Italy	1
Denmark	1
Germany	1
Egypt	1
Design:	
Longitudinal	3 (9%)
Cross Sectional	28 (91%)
Total sample size (n=30 Excl. duplicate samples)	921
Demographic & Clinical Characteristics	
Mean Age (n=27):	49.3
Age Range (n=16)	19-83
Mean % of females (n=29)	74.38%
Mean % of White Caucasians (n=12)	92.16% (Excl.one Egyptian study)
Mean MS Subtype % (pain & no pain samples)	(n)
Relapsing remitting	19 (62.25%)
Primary progressive	18 (15.79%)
Secondary progressive	16 (23.97%)
Mean MS Subtype % (pain only subgroups or samples)	
Relapsing remitting	(n)
Primary progressive	7 (53.91%)
Secondary progressive	5 (17.8%)
	5 (29.52%)
Mean Neurological Disability EDSS (mixed pain and no pain samples)	3.69 (n=8)
Mean Neurological Disability EDSS (pain only samples and subgroup	5.84 (n=6)
Mean time since diagnosis (years)	12.09 (n=19)
Mean % prevalence of pain across mixed pain and no pain MS samples	58.34% (n=12)
Mean % employment status (full or part-time) pain and no pain samples	40.7% (n=12)
Mean % employment status (full or part-time) pain only subgroups	36.5% (n=2)

END OF PUBLISHED ARTICLE

3.3 Systematic review erratum

Two studies included in the review (Kratz et al., 2011; Osborne et al., 2007) explored relationships between psychosocial factors and pain outcomes. However, some of the bivariate findings were not included in Table 2 and the main text of the published article because some of the more detailed subscales for pain-specific cognitions and behaviours were missed. Therefore, the following section will briefly summarise these findings, which will be discussed in relation to some of the decisions made for the cross-sectional study in chapter 5, and added to the updated MS pain model in chapter 6.

The erratum Table 1 shows the additional bivariate findings. The first outlines findings from a good quality study described in detail in chapter 1 (Kratz et al., 2011), which showed small to moderate bivariate negative correlations between pain interference and readiness to change (or maintain) task persistence behaviour. Specifically, pwMS who reported greater readiness to change in task persistence behaviour were more likely to report lower pain interference.

Second, as indicated in Table 1 of the published article, one good quality study (Osborne et al., 2007) showed that illness beliefs, affective and social beliefs, and task persistence/exercise coping behaviour, alongside other psychosocial factors, were strong predictors of pain intensity in a multivariate regression accounting for demographic and disease variables. However, the bivariate correlations were not presented in Table 2. Therefore, erratum Table 1 shows that pain severity shared a small significant negative correlation with pwMS' perceived control over pain, measured using the Survey of Pain Attitudes (SOPA) (Jensen et al., 1987), and was positively associated with the belief that one is disabled by pain. Pain interference shared a small to medium sized significant positive correlation with the pwMS' attitude that others should be solicitous in response to their pain behaviours. A medium sized negative association between pain interference and pwMS' belief that their emotions influence pain (considered to be an adaptive response), and a large positive association with perceived disability were also identified.

In terms of self-reported coping responses, measured using the Chronic Pain Coping Inventory (CPCI) (Jensen, Turner, Romano, & Strom, 1995), pwMS who rested more in

response to pain showed small to medium significant associations with greater pain severity and pain interference. Pain interference also shared a small to medium negative relationship with task persistence and exercise coping strategies, and a small to medium positive association with use of coping self-statements. In addition, medium to strong sized significant positive associations with guarding and resting coping responses were also identified. Other coping responses on the CPCI, such as asking for assistance, relaxation, seeking social support and pacing, did not show significant relationships with either pain outcome.

Overall, many of the bivariate relationships summarised were non-significant. However, those that were are incorporated into the refined model in chapters 5 and 6 to provide greater detail about some of the possible cognitions and behaviours that may contribute to pain and related disability in MS. Chapter 2 briefly highlighted there have been several ways of operationalizing pain-beliefs in MS, which are likely to overlap. Therefore, pain-beliefs that are similar to those identified in the SOPA were investigated using different measures in chapter 5.

These findings provide further support for the original MS pain model, highlighting the potentially important role of cognitive, emotional, behavioural and social factors, or processes in maintaining pain and related disability. The current model differs from Kerns' (Kern's 2000; 2002) broader stress and coping conceptualisation in several important respects. First, the model incorporates the content specificity of chronic pain models outlined in chapter 2 (Hasenbring & Verbunt, 2010; McCracken & Morley, 2014; Turk, Meichenbaum, & Genest, 1983; Vlaeyen & Linton, 2000), by including specific potentially modifiable cognitive, emotional, behavioural and environmental factors based on empirical findings from existing MS studies. Second, rather than focusing predominantly on predisposing vulnerability factors, the current model identifies factors or processes that are likely to maintain pain and related disability, and explores whether they are potentially helpful or unhelpful. Finally, the model explicitly distinguishes between neuropathic and non-neuropathic (musculoskeletal) pain subtypes, highlighting potential differences in the way pwMS respond psychologically to these experiences.

Table 1 Systematic review erratum: Psychosocial factors examined in relation to Pain Severity (PS) and Pain Interference (PI) in MS

Model	Psychological Factor	Quality	Design	Study Ref. (Table 1) and level of statistical techniques applied	Group differences, *r* correlations, odds ratios of PS & PI across studies - Average (range) (n=studies reporting sig.)	ANOVA & Regression (factors in combination with other psychosocial predictors & R^2 range across studies) (n= studies reporting sig.)
Factors from Operant Behavioural and Traditional Cognitive Behavioural Models of Chronic Pain (including Fear-Avoidance and Avoidance-Endurance, Motivational interviewing)	1. Readiness to change:	Good	Cross-sectional	14 (PI*)		
	Exercise				PI: *ns*	
	Task persistence				PI: -.30	
	2. Perceived importance:	Good	Cross-sectional	14 (PI*)		
	Exercise				PI: *ns*	
	Task persistence				PI:-.25	
	3. Pain attitudes (SOPA)	Good	Cross-sectional	24 (PS* & PI* as scales		
	Control			used in regression unclear)	PS:-.27 PI: *ns*	
	Disability				PS: .27 PI: .52	
	Harm				PS: *ns* PI: *ns*	
	Emotion				PS: *ns* PI: .29	
	Medication				PS: *ns* PI: *ns*	
	Solicitude				PS: *ns* PI: .29	
	Medical care				PS: *ns* PI: *ns*	
	4. Pain coping (CPCI)	Good	Cross-sectional	24 (PS* & PI* as scales used in regression unclear)		
	Guarding				PS: *ns* PI: .45	
	Resting				PS:.25 PI: .35	
	Asking for assistance				PS: *ns* PI: *ns*	
	Relaxation				PS: *ns* PI: *ns*	
	Task persistence				PS: *ns* PI: -.24	
	Exercise/Strength				PS: *ns* PI: -.19	
	Coping self-statements				PS: *ns* PI: .27	
	Seeking social support				PS: *ns* PI: *ns*	
	Pacing				PS: *ns* PI: *ns*	

CPCI: The Chronic Pain Coping Inventory; SOPA: Survey of Pain Attitudes; ns: non-significant.
*Uncontrolled bivariate correlation, uncontrolled comparisons (t-test /chi^2), principle component / cluster analysis
**Controlled bivariate correlation or comparisons, uncontrolled regression analysis
***Controlled multivariate analyses (ANOVA or regression)

Chapter 4 : A Qualitative Interview Study Investigating Pain and its Management from the Perspective of People with Multiple Sclerosis.

4.1 Chapter overview

In chapter 3 the systematic review demonstrated there is a growing body of empirical evidence focusing on the psychosocial correlates or predictors of pain severity and pain interference in MS. The majority of studies were cross-sectional in nature presenting mostly bivariate findings, although some accounted for key demographic and disease variables using multivariate analyses. The synthesis of evidence contributed to the development of a preliminary working cognitive behavioural model of MS pain. The model indicated that pain outcomes, including pain severity and pain interference, may interact with a range of potentially modifiable contextual and cognitive behavioural factors or processes, including pain-related catastrophizing, self-efficacy / perceived control, depression and anxiety. It also showed that pain acceptance, illness perceptions, thought suppression and perceived social support may also be important. However, in contrast to primary chronic conditions, fear-avoidance did not appear to be strongly associated with pain outcomes in MS.

Whilst the synthesis of reviewed evidence suggests that cognitive behavioural treatments may be beneficial for pwMS, there was generally a lack of good quality studies using temporal designs to investigate psychosocial factors or processes in relation to pain outcomes (Brochet et al., 2009; Khan, Amatya, & Kesselring, 2013; Newland et al., 2009). Therefore, we have little understanding of pwMS' experience of pain in relation to psychological responses across time. This is important because most pwMS are likely to experience a variety of potentially fluctuating and interfering painful symptoms (Seixas et al., 2014). This degree of unpredictability may influence pwMS' psychological responses in different ways and at different times, particularly as they encounter new or worsening symptoms. One way of capturing this dynamic process might be to conduct a longitudinal study investigating psychosocial factors and pain outcomes over time. However, another approach would be to use qualitative methods to ask pwMS about their lived experience of pain, and explore in greater detail their cognitive and behavioural reactions or responses, and efforts to manage pain. Most of the studies reviewed in chapter 3 investigated MS pain with quantitative designs, whilst

few have used qualitative methods (Douglas, Windsor, et al., 2008; Saverino & Solaro, 2010). In contrast to quantitative designs, qualitative methods are useful because they allow for a more open-ended exploration of pwMS' experience and beliefs about pain and associated treatments, which can highlight additional psychosocial factors or processes that have yet to be explored in previous quantitative studies. This is not only important to advance the development of the conceptual model and intervention, but may also improve our understanding of common themes and individual differences. The latter will allow us to think more carefully about developing patient-centred clinical approaches that aim to reduce the negative impact of pain and improve pwMS' engagement in other treatments. The current chapter presents a published article reporting on this next qualitative phase of work.

The preliminary MS pain model presented in systematic review was useful in highlighting the importance of several cognitive behavioural factors or processes in relation to pain outcomes. However, many studies explored depression in relation to pain, whilst fewer studies examined the role of more specific cognitive behavioural factors and processes. Correlational findings across the more specific factors and processes were also mixed, prompting several theoretical questions. First, the behavioural element of the model identified either non-significant or small effect sizes for fear-avoidance in relation to pain. This finding was surprising given that pain-related fear reflects a common response in primary chronic pain populations described in chapter 2. It may be this finding reflects the fact that two studies investigating this construct were either underpowered or of low quality. In addition, no studies in the review had explored other potentially unhelpful forms of behavioural avoidance, such as over-exertion or endurance responding. This was felt to be important in MS pain since research in MS fatigue had indicated "all-or-nothing" behaviour was a significant contributor to reduced functioning (Knoop et al., 2012; Skerrett & Moss-Morris, 2006). On the other hand, pain acceptance was identified as a potentially helpful response that shared a strong association with pain interference in one underpowered and unpublished study. Furthermore, although Kratz' et al.'s motivational model explored 'adaptive' task persistence and exercise management behaviours (Kratz et al., 2011), no studies had investigated other potentially helpful behavioural responses that may tap motivation, such as pwMS' flexible persistence with, or shifting to, a course of action guided by values and goals even in spite of pain (i.e. committed action). Therefore, asking pwMS more general qualitative questions about what they do in response to pain might

elucidate whether these behavioural responses were necessarily important in maintaining pain and related disability in MS.

Second, the cognitive part of the MS pain model indicated that pain catastrophizing was the strongest correlate of both pain severity and pain interference. Self-efficacy or perceived control also appeared to be relevant but to a lesser degree. However, whilst the model indicated that illness perceptions related to identity and chronicity may be important, no studies had explored beliefs specific to pain informed by Leventhal's common sense model of illness perceptions (Leventhal et al., 2003). Therefore, greater emphasis was also placed on developing open-ended qualitative questions around pwMS' pain-related beliefs in order to find out more about these, and other, perceptions that may be pertinent to MS pain. To develop a more integrated picture of PwMS' responses to pain, it was also felt that asking them how they think about pain in conjunction with what they do might be informative for the model.

Although a few studies in the review showed that correlational findings for neuropathic and non-neuropathic pain subgroups were mostly comparable, another gap in the model centred on the limited understanding of how a person may differentially respond to painful symptoms. It was therefore unclear whether one particular symptom stood out as being more problematic than others. In addition, the review provided very little information about how pain may interact with other MS symptoms, which was emphasised in Kerns' earlier diathesis stress model (Kerns et al., 2002). Therefore questions also explored both of these aspects. Finally, although the operant behavioural elements related to perceived solicitude or social support were identified in the review, they only shared small to medium associations with pain outcomes. It was therefore felt that exploring other people's reactions in response to pwMS' pain might provide more detailed information about the social element of the model.

This chapter is published in the following article:

Harrison, A.M, Bogosian A., Silber, E., McCracken, L.M. and Moss-Morris, R. (2014). "It feels like someone is hammering my feet": Understanding pain and its management from the perspective of people with Multiple Sclerosis. *Multiple Sclerosis*, 21 (4):466–76. DOI: 10.1177/1352458514544538
http://msj.sagepub.com/content/early/2014/08/04/1352458514544538

4.2 Published article

Article type: Original Article

Article title: "It feels like someone is hammering my feet": Understanding pain and its management from the perspective of people with Multiple Sclerosis.

Authors:
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Keywords: Multiple sclerosis, pain, experiences, management, qualitative, thematic analysis

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Abstract

Background: Pain affects around 63% of people with Multiple Sclerosis (pwMS). Biomedical treatments demonstrate limited efficacy. More research is needed to understand pain from the individual's perspective in order to better inform a patient-centred approach that improves engagement, self-management and outcome.

Objective: To explore pwMS' experience and responses to pain, and their perspectives on pain management.

Methods: Twenty-five, in-depth, semi-structured, telephone interviews were conducted. Interviews were audiotaped, transcribed and analysed using an inductive thematic analysis approach with elements of grounded theory.

Results: Key themes included vivid descriptions of pain and beliefs that pain is unpredictable, a sign of damage and may worsen. Anger was a common emotional response. Two dominant pain management themes emerged: one related to pain reduction and another to acceptance. Those focussing on pain reduction appeared to engage in cycles in which they struggled with symptoms and experienced continued distress.

Conclusion: Findings identify pain-related beliefs, emotional reactions and disparate pain-management attitudes. All may influence pwMS' responses to pain and what they ask of their clinicians. Uncovering pwMS' personal beliefs about pain, and introducing a broader biopsychosocial understanding of pain in the clinical context, may provide opportunities to rectify potentially unhelpful management choices and enhance pain acceptance.

Introduction

A recent meta-analytic review estimates pain affects around 63% of people with Multiple Sclerosis (pwMS) (Foley et al., 2012). MS pain can be broadly classified as either neuropathic, directly caused by a primary lesion or disease of the somatosensory nervous system (including Lhermitte's sign and trigeminal neuralgia), or non-neuropathic, arising from actual or threatened damage to non-neuronal tissue including activation of nociceptors (musculoskeletal) (Merskey & Bogduk, 1994; O'Connor et al., 2008). Pain can be indirectly related to MS, coincident, or caused by other MS symptoms and treatments (Pöllmann & Feneberg, 2008). A third of pwMS describe pain as one of the worst MS symptoms (Stenager et al., 1991). Many experience uncontrollable pain (Kerns et al., 2002) and current biomedical treatments demonstrate limited efficacy (Beard et al., 2003).

MS pain is yet to be carefully understood or extensively studied within a broader biopsychosocial framework (Douglas, Windsor, et al., 2008). Whilst there is a growing body of evidence for psychosocial factors associated with MS pain (Douglas, Wollin, et al., 2008; Osborne et al., 2007; Osborne, Turner, et al., 2006), few studies have engaged patients in direct discussion about their experience. Two qualitative studies offer useful insights into pwMS' descriptions of pain and its impact (Douglas, Windsor, et al., 2008; Saverino & Solaro, 2010). However, little is known about pwMS pain-related beliefs, which may be important since the way individuals conceptualise their MS symptoms (Jopson & Moss-Morris, 2003; Riazi, Thompson, & Hobart, 2004; Vaughan, Morrison, & Miller, 2003) and treatments (Martin et al., 2014) can determine self-management behaviour and outcome. Therefore, using qualitative methods to better understand how individuals perceive pain may guide the development of patient-centred clinical approaches that improve engagement in specific treatments.

The aim of the current study was to explore pwMS' experiences of pain and their beliefs about pain and its management.

Participants and methods

The project was approved by the Berkshire Research Ethics Committee.

Participants were included if (a) they were over eighteen years of age, b) diagnosed with MS, and c) had experience of pain in the context of MS. PwMS were excluded if they were non-English speakers.

Recruitment was via national advertising and through National Health Service (NHS) MS clinics. Potential participants were invited to complete a screening questionnaire, including demographics, Self-report Leeds Assessment of Neuropathic Signs and Symptoms (S-LANSS) (Bennett, 2001), MS subtype pictorials (Lublin & Reingold, 1996) and Self-administered Expanded Disability Status Scale (Bowen, Gibbons, Gianas, & Kraft, 2001). Once returned, purposive sampling was used to select a diverse range of participants. Thirty-two responders to study advertisements returned the screening questionnaire and 26 from MS clinics. Twenty-five participants were interviewed (Table 1): 12 from the MS Society and 13 from NHS specialist clinics. Interviewing ceased once data saturation was reached, defined as the point at which no new information or themes are observed in the data (Guest, Bunce, & Johnson, 2006).

Table 1 Characteristics of the sample (*n*=25)	
Characteristics	Number (%)
Sex:	
Male	6 (24)
Female	19 (76)
Age (years):	
18-30	4 (16)
31-40	5 (20)
41-50	5 (20)
51-60	5 (20)
61-70	6 (24)
Ethnicity:	
White-British	17 (68)
Black African-British	2 (8)
Black Caribbean-British	2 (8)
Asian-British	2 (8)
Mixed (White-Asian)	2 (8)
Years of education:	
1-11	3 (12)
>12	22 (88)
Employment Status:	
Full-Time	2 (8)
Part-Time	9 (36)
Full-Time Education	1 (4)
Unemployed	7 (28)
Retired	6 (24)
MS Subtype Pictorials:	
Primary progressive	3 (12)
Secondary progressive	6 (24)
Relapsing remitting	16 (64)
Experiencing current relapse:	
Yes	1 (4)
No	22 (88)
Not Sure	2 (8)
Neurological Disability Self-Report EDSS:	Mean (SD) (Range) 5.68 (.98) (4-7)
Current MS Symptoms:	
Fatigue	23 (92)
Bowel or bladder dysfunction	4 (16)
Balance disruption	23 (92)
Cognitive impairment	19 (76)
Blurred or double vision	12 (48)
Difficulties with Speech	17 (68)
Difficulties with swallowing	16 (64)
Stiffness and spasms in muscles	20 (80)
Tremor	10 (40)
Sexual dysfunction	10 (40)
Time Since Diagnosis (years):	
1-10	13 (52)
11-20	7 (28)
21-30	5 (20)
Pain Severity 11-point Numerical Rating Scale (0 'no pain' and 10 'pain as severe as it could be')	Mean (SD) (Range) 6.58 (Moderate) (1.98) (3-10)
Pain Type (S-LANSS)[1]	
Non-neuropathic (≤11)	8 (32)
Neuropathic (≥12)	17 (68)
Recruitment Source:	
NHS Specialist Clinics	13 (52)
MS Society UK	12 (48)

[1] This is an approximation based on a self-report measure not yet validated in the MS population

Participants included six men and nineteen women, with a mixture of ethnic backgrounds, ages and occupational status. PwMS reported an average pain severity rating of 6.5 on the S-LANSS 11-point scale suggesting pain in the moderate to severe range (see Table 1 for further demographic and disease information).

Design

Non-directive, semi-structured telephone interviews were conducted by A.H. to elicit accounts of participant's experience. The interview schedule (Table 2), piloted and edited by three patient and public involvement members with MS, included seven open-ended questions, encouraging individuals to share issues that were important to them. Questions were provisional and modified if more clarification was required. Telephone interviews were used to improve access to pwMS who might otherwise be excluded due to severe disability. Interviews ranged from 30-60 minutes in duration, and were digital-audio recorded and transcribed verbatim. Once data saturation was reached, those who consented but were not interviewed were thanked for their time, and given the opportunity to participate in future studies in this research programme.

Data analysis

Data were analysed following established guidelines for inductive thematic analysis (Braun & Clarke, 2006) and procedures from Grounded Theory (Glaser & Strauss, 2009), used specifically to gain psychological insights to guide the next stages of the MS pain treatment research programme.

A.H. listened to interviews, and repeatedly read transcripts to become immersed in their content. Coding was undertaken with regular discussion with authors A.B. and R.M.M., who read and coded excerpts from four transcripts to ensure AH's coding was grounded in the data. Each unit of coding was assigned a descriptive name on Nvivo 10 software, and wherever possible, reflected participant's vocabulary (Glaser & Strauss, 2009). Codes were redefined and combined, and new and alternative codes were generated (Glaser & Strauss, 2009). Broader themes were identified and organized into a preliminary framework. A.H.'s written accounts and diagrams of themes and their interrelationships were repeatedly checked against transcripts to ensure they accurately

represented the data (Patton, 1990). An audit trail of coding and thematic developments was maintained.

Table 2 Interview Schedule

Questions	Prompts
Can you tell me about the pain you experience?	How would you compare these different kinds of pain?
How would you view your pain in relation to other MS symptoms?	Where does pain fit in? How do you rate you pain compared to other symptoms? How does pain affect your day-to-day life compared to other symptoms?
Health care professionals have certain views and beliefs about pain. I am interested to hear about your personal beliefs or views about your pain?	Things that make pain worse or better, causes curing or controlling, consequences, how long do you think you will have MS-related pain?
Tell me what you usually do when you experience pain?	How would you usually react, similar reactions for different types of pain?
Can you describe how you deal with your pain?	Concrete example / a typical day, most helpful things, least helpful, how effective, similar for all kinds of pain?
How do others (i.e. family or friends) react to your pain?	Concrete example?
What do you think could be done to help you with your pain?	Do you think anything else should be offered to you? What should be addressed in treatment? How might services assist you? What might a treatment look like / target? How might you expect to feel after a fictitious pain management treatment? How would know the outcome was successful?

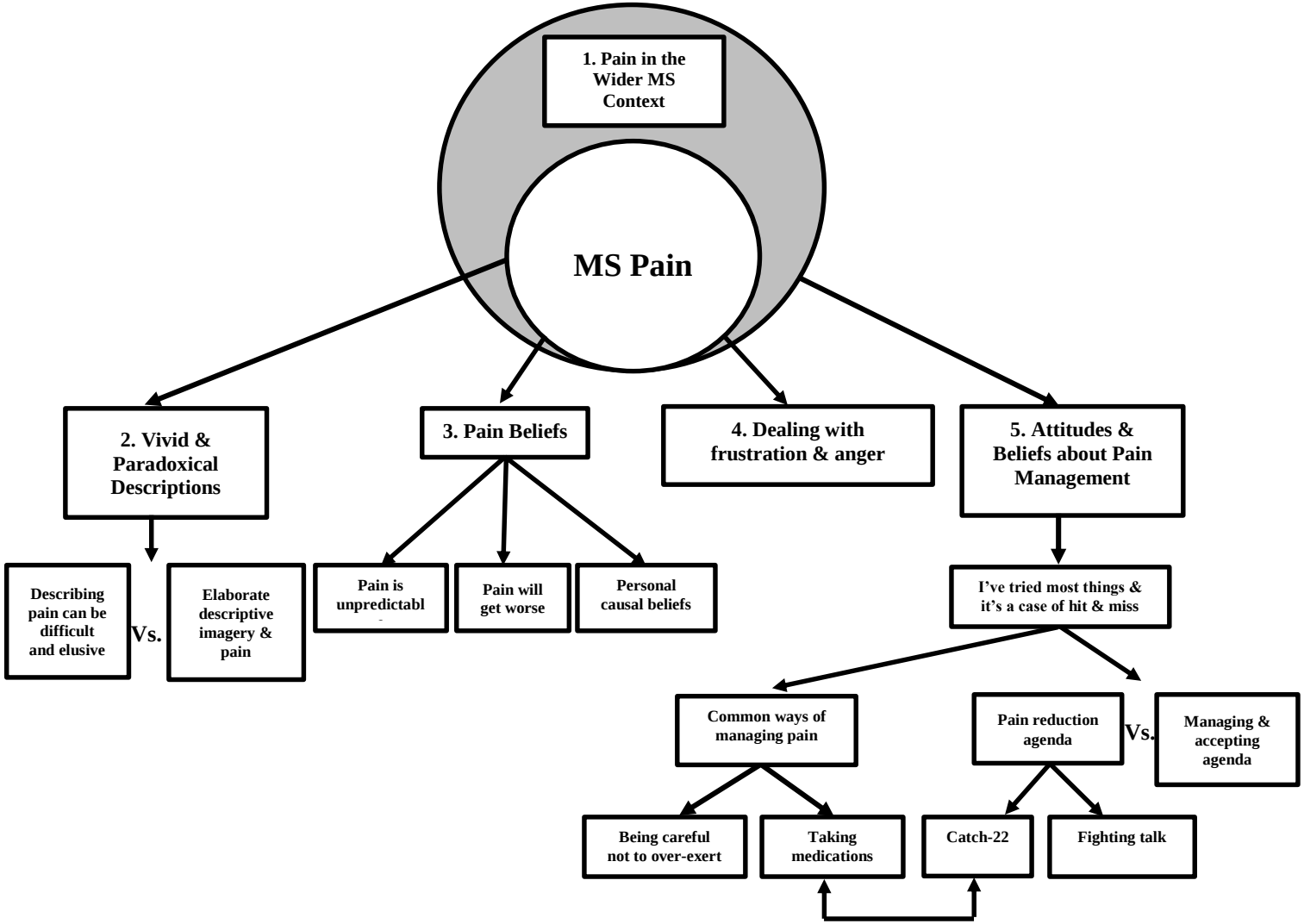

Figure 1: Thematic diagram of key themes and subthemes

Results

Figure 1 summarises five key identified themes and their subthemes: 1) Pain in the context of MS, 2) Vivid & paradoxical descriptions, 3) Pain beliefs, 4) Dealing with frustration and anger, and 5) Attitudes & beliefs about pain management.[5] Each of these is described in turn and a summary provided in table 3 with additional examples of coded quotes.

[5] More detailed information of all the themes can be obtained from the authors [see Appendix E for coding manual].

Table 3 Key Themes: additional Examples

Themes and Subthemes	Example Quotations
1. Pain in the wider MS context	*"I think it is all just swirled into one… MS pain is wrapped up with a lot of other things."* *"Everything comes together. They [symptoms] all happen around the same time, and that normally starts to occur the more tired I get."*
2. Vivid and Paradoxical Descriptions	*"Like pins sticking into my toes."* *"Feels like somebody has just stood on my hands."* *"Imagine a hundred times worse than you could squeeze in a bear hug."* *"It's really hard to describe these things!"* *"I am not too sure how it feels or how to describe it… I think that I have only recently understood how it feels."*
3. Pain beliefs	
Personal causal beliefs	*"The lesions on the brain… they are putting pressure on certain parts of the brain, I think that causes a bit more pain in that certain area."* *"When I have the lower back pain, it's obviously got something to do with the nerves in that area, it can't be anything else."* *"Pain is like the brain or my nerves are saying, okay you need to do something different."*
Pain is unpredictable	*"So I'm taking it [Simvastatin], not for pain but for high cholesterol, and it may have affected my pain."* *"It's so unpredictable and you have no idea when and where, if and how."*
Pain will get worse	*"There is no way I could point to a diary and say it is going to happen then it's just decides "okay, we are going to do this today."* *"I envisage it getting worse."* *"I think I see it every day, you know what that path is, I am not getting any better, and the intensity is a bit more as time passed."*
4. Dealing with frustration & anger	*"When I get my everyday pain, as I call it, it's just like – it's an annoyance, it's just there and it's like, oh, okay then!"* *"Oh, I just find it frustrating because I can't do the things that I want to do."* *"I went to the pictures the other day to see a film and you get involved in it for a certain time and then your mind wanders because you think, will this F-ing pain ever go away?!"*

5. Attitudes & beliefs about pain management	
I've tried most things and it's a case of hit and miss	*"It's been hard to control because there is… something that will work on me, and then there are some things that don't, and they will work for a certain amount of time, and then it won't work."*
Common ways to self-manage	*"Well if it is really bad, I just stay in bed and I rest."*
Pain reduction agenda	*"Find me a wonder drug for pain."*
Fighting talk	*"I'm not very good at giving in to things and… I'm not very sensible sometimes."*
Catch-22	*"The actual painkillers and medication you take can end up debilitating you just as much as the pain."*
Management and acceptance agenda	*"I will have to adapt to leading my life with it there".*

1. Pain in the wider MS context

This first theme explains that many participants viewed pain as the worst symptom of MS. PwMS described pain as inherent to other MS symptoms, including optic neuritis, spasms and sensory dysfunction. The co-occurrence and interaction between pains, fatigue and sleep disruption were also highlighted. A few pwMS suggested that pain had become a common label to identify or describe other MS symptom experience.

I think it's all just swirled into one… MS pain is wrapped up with a lot of other MS symptoms. All symptoms around my legs seem to have some sort of pain attached to them… I think a lot of my symptoms have now become about pain. (Female, 46 RRMS)

2. Vivid and Paradoxical Descriptions

Although many patients said pain was hard to describe, most in fact provided clear descriptions. Many of these descriptions also included strong imagery.

In my feet, you know, I could say that um it feels as though somebody is um hammering my feet with a claw hammer, a metal hammer… but how do I know that because that has never happened to me?
(Male, 62, PPMS)

3. Pain beliefs

Three types of pain-related beliefs were prominent.

Pain is unpredictable. Many participants suggested their pain had no discernible pattern, arising randomly from day-to-day and changing unpredictably across the disease course.

It changes quite a lot with MS. I get these feelings in my toes… it feels like there are pins sticking in… and the pains change as well, and all the feelings in the feet change. It's become more painful over the last year than it was before. (Female, 58, RRMS)

Personal causal beliefs. PwMS expressed a variety of personal causal beliefs about pain, ranging from the use of cholesterol medication to having a stressful lifestyle.

I would definitely say… the main thing is stress… stress really flares it up. (Male, 35, RRMS)

Pain was sometimes assumed to be a direct result of damage to nerves and viewed as a sign or omen of worsening pain, further damage, relapse and disease progression. Some pwMS felt this explanation came from HCPs.

I have been told by neurologists it's to do with the scarring on the right-hand side of my brain [headaches]. *I've had quite a few MRI scans that have shown up where the areas of the… damage, the myelin sheath are, and I experience quite serious headaches… I don't know whether I believe if it's a pain more telling me to calm things down a bit or whether it's something going wrong with my nerves.* (Female, 42, SPMS)

PwMS sometimes referred to vivid causal descriptions of the central nervous system being confused or faulty.

I know that a lot of it is caused by… the electrical cable of your nerves, the myelin has holes in the plastic sheath around a cable and so it isn't working properly, some of the signals are not getting through… that's when it ends up causing pain. (Female, 55, RRMS)

Pain will get worse. Most pwMS' felt that pain would worsen over time.

Well, I'm expecting… it does, it has got worse… over the past say five or six years, walking distances is more and more difficult. So I'm imagining that it will get worse, hopefully not too quickly because my progress has been quite steady over the years. (Male, 52, RRMS)

4. Dealing with frustration & anger

The fourth subtheme reflects the idea that pain is an unwanted companion for pwMS, often resulting in frustration and anger. Many described these difficult feelings were due to pain's intrusive and unrelenting nature, becoming a central focus in their awareness.

The discomfort causes frustration. The best way to describe it is… when… something is just… like a dripping tap or something, it's just like, 'Oh god why is this…? Just go away!' kind of thing.
(Male, 35, RRMS)

Most reflected on pain's ability to prevent spontaneous or planned engagement in enjoyable activities. This aroused frustration and anger, and some highlighted a tendency to dwell on pain and an inability to disengage from angry feelings.

If I go for a walk with my friend… after half an hour, I know I can feel pain increasing… I can feel myself getting upset and cross and then I have to sit down and wait… that makes me really angry … if I go home and dwell on that… and if it doesn't recede, then I get more angry and upset. (Female, 46, RRMS)

Some described becoming short-tempered towards others, which resulted in socially isolating behaviour to manage pain and preserve relationships.

I get really grumpy… to the point where nobody can talk to me because I'm so 'ahhhhhhh, leave me alone!' and let them know everything is painful. I feel guilty about it afterwards (Female, 38, RRMS)

Other causes of anger and upset arose from disappointment with recurrent, unsuccessful attempts to reduce pain with medications. A few felt treatments specifically addressing anger may be helpful.

5. Attitudes & beliefs about pain management

The fifth subtheme illustrates how pwMS shared mixed successes in attempts to reduce pain.

I've tried most things and it's a case of hit and miss. PwMS used a variety of treatments and management strategies, ranging from medications and self-administered physical strategies (e.g. bathing or stretching) to mental visualization or distraction techniques.

With my headaches, it's been quite hard to control because there is… something that will work on me, and then there are some things that don't, and they will work for a certain amount of time, and then it won't work. (Female, 18, RRMS)

Common ways to self-manage. While a minority of pwMS used exercise to reduce pain arising from standing or sitting still, the majority identified two common ways to self-manage, including taking pain medications (even if ineffective) and being careful not to over-exert themselves by stopping and resting regularly.

Pain reduction agenda. When asked about expectations of future treatments, many professed adherence to a pain reduction agenda, reflecting an eagerness to try new 'wonder drugs' and learn new 'mental tricks'.

Just relief from the pain… so I don't have it anymore, or if I do, that it's less than what I have been experiencing that has to be the ultimate goal, I can't think of anything else… I would want the pain to be less or non-existent - it has to be! (Female, 38, RRMS)

Catch-22. Consistent with the reduction agenda, pwMS often described unique 'Catch-22' situations or unhelpful 'cycles' that undermined common ways to self-manage**.** Figure 2 shows how one lady's attempts to manage or reduce pain (avoiding movement), in combination with other debilitating symptoms (fatigue), tended to result

in worsening pain and symptoms, and additional problems (weight gain). This often equated to pwMS feeling increasingly stuck.

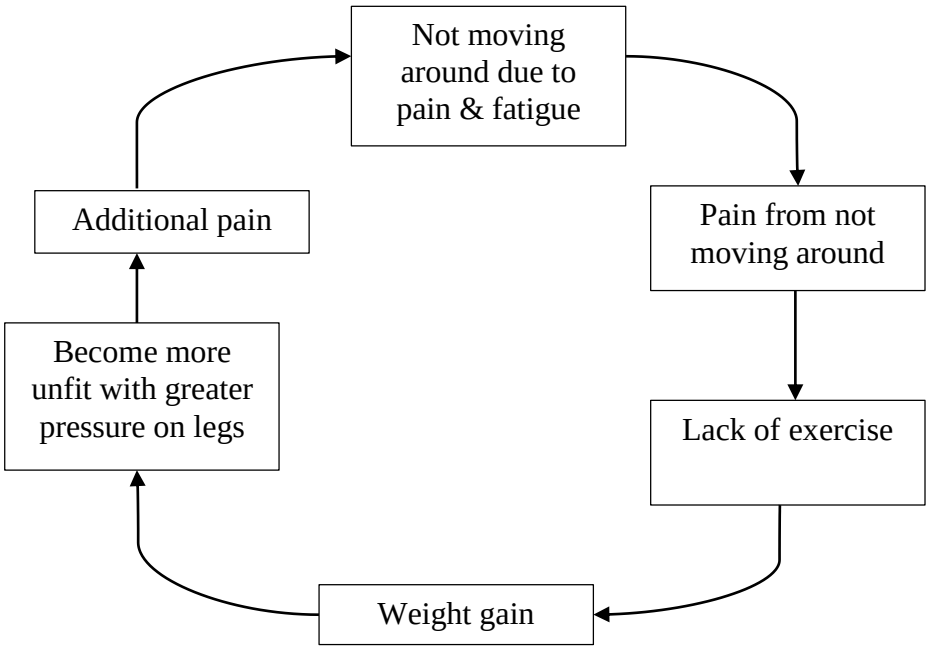

Figure 2: Catch-22 example (60 year-old Female, RRMS)

Fighting talk. The same pwMS often described themselves as 'fighters', suggesting they needed to think positively or be a 'positive person'. For some, motivation for their struggle reflected the desire to remain independent and overcome the inclination to avoid everyday activities.

I don't like that idea at all [loss of independence], *that is to me the worse consequence and … I mustn't think about it because… I'm a fighter and I will fight as much as I can… Now, once I can't… that doesn't bear thinking about.* (Female, 62, PPMS)

For others fighting was about problem-solving their pain and MS, or an internal battle focussing on the pushing away of thoughts related to their disease progression, sometimes rejecting advice offered by HCPs and family members (e.g. over-exerting when resting has been prescribed). One participant with long-standing pain explained that improved pain management was about understanding when to fight and when not to.

You can't fight it; you just go with it. When I talk to a friend of mine about her problems, I say to her well… today is one of the days you can't work through it, you have just got to go with it. We're not these kind of defeatist people, we like to… hold our own… but you can't. (Male, 45, SPMS)

Managing and accepting agenda. In contrast others felt adapting or planning a lifestyle to fit with pain was more realistic. This reflected the view that curing pain and MS was unlikely. Accepting pain as part of life, being in touch with the body and knowing one's limits were viewed as integral to improved management.

The thing is you can't cure it can you, so it is all about management… managing yourself and knowing what medications to take at what time… a lot of it is pain management rather than pain curing. (Male, 35, RRMS)

Discussion

This study provides a unique insight into the experience of pain in the context of MS. PwMS identified pain as part of a conglomerate of interacting symptoms where it was often hard to separate pain from sensations such as numbness, stiffness and fatigue.

Most pwMS interviewed for this study provided vivid and sometimes dramatic descriptions of their pain to convey the intensity of the pain experienced. PwMS viewed pain as unpredictable, uncontrollable and attributed a variety of potential causes. Detailed descriptions of damage to nerves or 'wiring' were often recounted, sometimes in conjunction with ominous beliefs about worsening pain, other MS symptoms and disease progression (Douglas, Wollin, et al., 2008). Pain catastrophizing is associated with poorer outcome in patients with chronic low back pain (Foster et al., 2008). A recent study has shown patient's MS illness perceptions are associated with pain severity and interference (Spain et al., 2007). However, pain-specific illness perceptions have not been explored in relation to MS pain.

Consistent with the primary chronic pain literature (Fernandez & Turk, 1995), pwMS frequently reported frustration and anger, which worsened when faced with limitations preventing planned and spontaneous activity. Anger was expressed in conjunction with themes of unpredictability, dissatisfaction with pain medications and HCP interactions.

Some described an inability to disengage from difficult feelings, expressing a desire to manage anger more effectively.

PwMS employed a range of management strategies to reduce pain or associated distress, often with mixed results. This is consistent with the finding that medications for neuropathic pain may benefit some, but not all individuals, with other chronic pain conditions (Kalso et al., 2013), and a study (Heckman-Stone & Stone, 2001) showing that pwMS ranked pain medication as the most *effective* and *ineffective* coping strategy, and exercise, rest and sleep were identified as common ways to self-manage. More importantly, our findings revealed pwMS' attempts to manage pain using these common strategies often resulted worsening of others and unhelpful 'catch-22' vicious cycles.

Attitudes towards management were split between those who focused on reduction of pain, where pain was viewed as something to be fought, and those who felt management was about acceptance and adapting to a life with pain. Acceptance is a key predictor of adjustment in MS (Pakenham & Fleming, 2011). *Pain acceptance*, defined as willing engagement in activities, in a way that includes contact with pain, without attempts to struggle with or control it, is also a predictor of better functional outcome in primary chronic pain conditions (McCracken, 2007; McCracken & Velleman, 2010). PwMS who talked more about acceptance expressed a preference for a more holistic biopsychosocial approach to pain management. In contrast, the majority held a more mechanistic biological account of cause (e.g. 'bad nerves', lack of medication, external stressors) and talked more about the need for 'wonder drugs'. This split in attitudes might also reflect a recent study showing that chronic pain subgroups held distinct models of causal interpretation of pain that were consistent with views of how it should be treated (Martin et al., 2014). It therefore seems important to examine the role of pain acceptance and broader causal schemas of pain and management in MS.

Implications for treatment

Some pwMS explained their biomedical interpretations of pain were provided by HCPs (particularly related to causes and control beliefs). Such interpretations may influence patient's to rely on medications which to date show limited efficacy. While health professionals are unlikely to have the time to replicate an in-depth interview exploring pain, it may be beneficial to provide a broader biopsychosocial understanding by asking

a few targeted questions centring on pain and management beliefs. For example, a patient with recurrent (perhaps vivid) thoughts that pain is associated with increased damage to nerves (e.g. 'if I push myself I'm going to damage myself even more') may begin to avoid everyday activities. While such thoughts may be protective in certain contexts (e.g. not over-exerting during an exacerbation), they are likely to be unhelpful if followed as generalised rules. Therefore, orienting patients to a biopsychosocial perspective of pain via psychological interventions that actively target pain beliefs and distress by exploring their validity (an aim of traditional Cognitive Behavioural Therapy, see Eccleston et al., 2009), or changing the person's relationship to their mental and bodily experience (Acceptance-based approaches, see Veehof, Oskam, Schreurs, & Bohlmeijer, 2011), may lessen their influence on behaviour, by interrupting catch-22 cycles. Since pwMS describe pain as interacting with other MS symptoms within vicious cycles (with some possessing their own psychosocial consequences (Knoop et al., 2012), it may be that a broader symptom management strategy, rather than a pain-specific one, is necessary.

There were several limitations with this study. A single data-gathering period cannot elucidate the variable and every changing presentation of MS pain. Therefore, future research may benefit from an ongoing assessment across the course of illness by conducting a series of interviews tracking the individual's beliefs across time, identifying factors pertinent to functioning. Because recruitment focused specifically on participants with pain participants may have experienced higher than average pain severity. Pain ratings in this study were in the moderate to severe pain on average. Other MS studies using similar measures commonly report average pain ratings of 'mild to moderate (Osborne, Turner, et al., 2006). As with all qualitative research interviewer demographic characteristic could have influenced the interview process. However, use of telephone interviews, carefully constructed open questions and the fact that the interviewer was independent of patients' health care will have reduced this bias. It is also possible that prior knowledge of psychological models of pain may have influenced the salience of certain themes reported potentially resulting is less emphasis being placed on alternative explanations for the data collected. The exclusion of non-English speakers may mean findings do not extend to pwMS from different cultural backgrounds.

Overall, our data indicate there may be benefits to talking through pain- and treatment-related beliefs with pwMS. This process may uncover pain-related anger, and provide the opportunity to rectify idiosyncratic pain-beliefs, which influence ineffective management strategies and perpetuate vicious cycles of distress and reduced functioning. Future quantitative research would enhance our understanding of these key issues within a representative sample, observing changes using a longitudinal design.

Acknowledgements

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END OF PUBLISHED ARTICLE

4.3 Qualitative study erratum

One aim of the qualitative study was to develop a better sense of how pwMS perceived other's responses to their pain. However, a sixth theme centring on the social aspects of pain was omitted from the published article because of the short word limit imposed by the journal. It was also the case that this theme had already been well described in the previous qualitative literature (Douglas, Windsor, et al., 2008). For the purposes of this thesis, and intervention development, the following section briefly describes these additional findings, which are incorporated within the refined MS pain models in chapters 5 and 6.

6. Pain is invisible to others

When pwMS were asked either about the impact of pain or others responses to it, many said that they felt that pain was invisible to others. They often explained that the lack of clear visual physical damage or injury to the body often resulted in others failing to understand or appreciate the extent of their pain.

"Because it's something people can't see... You know, if somebody's walking around with an arm in a sling or plaster on their arm or leg, people go, oh you've broken your leg." (Female, 63, SPMS)

"I will tell you one thing, work can be difficult, one of the biggest problems with going to work is that people don't understand it, they can't see it because you know when people have got pain they have normally got a sling on, or an eye patch, or they have got stitches, you know, something to represent their pain, and when you go in and you look healthy, and you try to say to people, well I don't feel well, they will say, well you look fine to me." (Female, 55, RRMS)

In some cases pwMS felt that the invisibility of pain often lead to them feeling as though others were questioning the legitimacy of their experience, which even occurred when they tried to describe it to others.

"But looking at me, listening to me, pain and anything else… No, I don't think it goes in, it doesn't, it's what people can see and they judge you on what can be seen rather than what you're telling them."
(Male, 35, RRMS)

Although the invisibility of pain was distinct from other themes identified in Figure 1 of the published article, it was closely linked to pain being difficult to describe, and often related to feelings of anger and frustration. This theme also encompassed another subtheme, which reflected pwMS' tendency to be more selective in their decision to 'conceal or reveal' pain to others.

"Um, well [chuckling] *they react differently I suppose, my close friends, it's about how much you tell someone isn't it, so some people I chose to tell and others I don't and so they can never understand if I don't tell them, I don't want - I am sort of torn between, it sounds ridiculous, because how can they help me if I don't tell them but I don't see that everybody needs to know about the MS or the pain."* (Male, 45, SPMS)

Sometimes pwMS 'concealed' pain because they felt others would not understand, or were concerned about what others would think about them.

"Purely because pain – like fatigue – is one of those things that people can't see so they can't relate. They can see you might have pain, the expression on your face, but a lot of MS sufferers, if they get pain, they try and hide it. So they are fighting it on that level and then they are fighting it from people seeing it at another level. So I think that makes people worse because they are worried what people are going to think."
(Male, 45, SPMS)

On the other hand, a few pwMS felt that talking about pain was unfair on others, particularly when it was potentially distressing for them.

"I don't like people to know that I'm suffering pain because, I mean, it's just not fair for other people to do that [I: Can you say more about that?] …When I've talked to other people about this I'm very reluctant, as you have gathered to talk about how the intensity of the pain and how much I feel and whatever, I just don't like it to impinge on my life or on the life of others and that's my main objection to it… They've [family]

seen it over the years and they've watched me cope with it and they can't help and that's very distressing for them at times." (Female, 53, RRMS)

In addition, some individuals said they were uncertain why they had been so reluctant to share their experience.

"When I do experience pain and I have been unwell, I don't really go out and I don't think I am open with my MS or my pain, I'm quite a closed person, it's not something that I would tell anybody else, unless I have a good relationship with them, like I don't really open up about it. (Crying) [I: May I ask why that might be, from your perspective?] Um, I am not sure, I didn't think it was deliberate, I don't know why, I haven't really thought about it." (Female, 28, RRMS)

However, in some cases pwMS felt that selectively 'revealing' their pain experience to others had some benefit, including making them feel less depressed and helping them to work around pain when taking part in shared social activities.

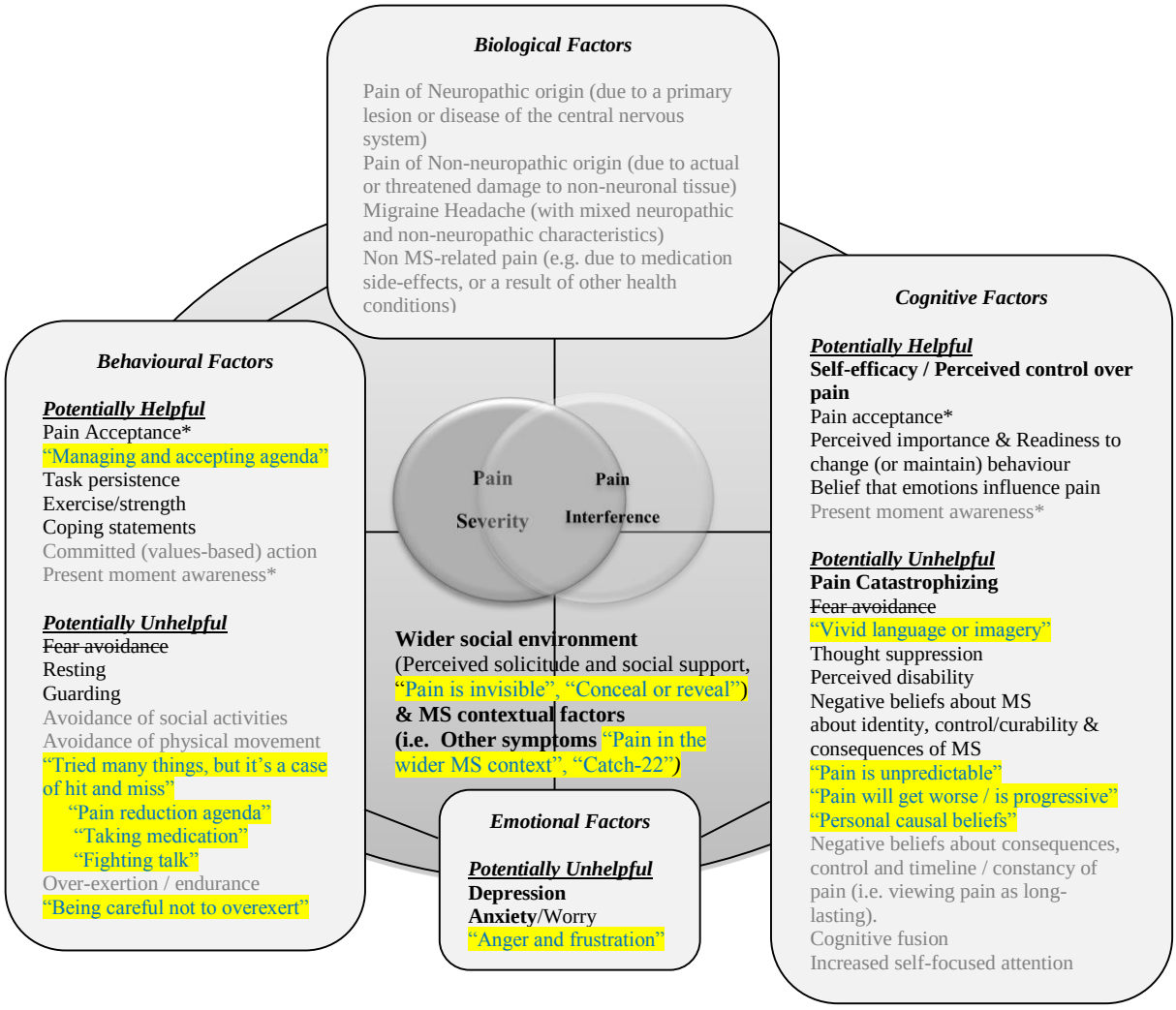
"Most of my friends have been really supportive and understanding, they find it quite hard to get their heads around it. So the girl I have just been out with this morning, she's a really good friend, so she completely knows that I can only walk X far, so we only walk to the tree that we have earmarked that we can go to, you know, and then we get a coffee and that's all fine because that's what we always do. So that feels, that's not, somehow that's not depressing and I talk a lot about the MS with her, and I have got five or six really, really close friends that I talk to about it a lot, and then I have got other friends I don't talk to about it at all." (Male, 45, SPMS)

Overall, the finding that pwMS felt pain was invisible to others, or should be concealed in certain situations, may have some important emotional (e.g. frustration, anger and depression) and behavioural consequences (e.g. not expressing emotions related to pain, angry outbursts or withdrawal). Therefore, these themes have been incorporated into the updated pain model in chapters 5 and 6 to improve our understanding of how some of the potential social behaviours and emotional consequences may interact and contribute to worsening pain and related disability in MS. Collectively, these findings also contributed to the development of a new treatment.

Chapter 5 : A Cross-sectional Study of Cognitive and Contextual Behavioural Correlates of MS Pain.

5.1 Chapter overview

In the previous chapter the qualitative study explored pwMS' experience of pain and how they manage it in greater detail. Several important findings emerged from this work, which have been incorporated within the updated working theoretical model of MS pain below (see Figure 7).



Bold text = strong evidence, with many studies conducted with studies consistently supporting this role.
Normal text = weaker evidence, where findings appear to be consistent but studies are few.
Grey text = factors that may play an important role in primary chronic pain theories but have yet to be investigated.
~~Strike-through text~~ = moved or considered less important and therefore removed
Highlighted text = new factors, processes and other findings in the model
Blue text = salient qualitative themes from chapter 4.
The above maintenance model is assumed to be interactional rather than unidirectional
*Pain acceptance and present moment awareness have a significant behavioural component and, therefore, are represented as both a cognitive and behavioural process in our model.

Figure 7: Updated Conceptual Model of MS Pain (Diagram taken from Harrison, McCracken, Bogosian, & Moss-Morris, 2015)

The original model from the systematic review indicated that several behavioural responses may potentially be important in the context of MS pain. First, one of these responses included experiential avoidance of pain (the inverse of pain acceptance) from ACT's psychological flexibility model, which is an important correlate in primary chronic pain samples (McCracken & Morley, 2014). A collection of themes and subthemes from the qualitative study around pwMS' disparate pain management attitudes suggested that pain acceptance may be a protective process in MS. On the one hand, many individuals sought pain reduction, tried different pain management strategies, often with limited success, took medications even when they found them to be ineffective, and struggled with pain or feelings of anger, which often made them feel worse. On the other hand, a few individuals felt that factoring pain into their lives without trying to "fight it" were less likely to report feeling caught up in vicious cycles that amplified other MS symptoms and distress (i.e. "Catch-22").

Second, whilst fear-avoidance appeared less important in the original model based on the review and qualitative study, most pwMS suggested they were "careful not to over-exert" themselves either for fear of making pain worse or needing to rest for prolonged periods afterwards to recover. It was therefore unclear whether pwMS had problems with avoidance in the context of fear, were persisting with tasks to the point where it was unhelpful, or engaged in both responses. Whilst effects for fear-avoidance were generally small or non-significant in the review, other studies indicated that avoidance behaviours may be important (e.g. guarding and resting). Therefore, it is possible that avoidance is not only related to fear of activity, but rather it could also be related to other thought processes. For instance, avoidance might be driven by fear of making symptoms worse, catastrophic thoughts about pain and other symptoms, beliefs that resting is helpful, or negative affect (e.g. frustration or anger). It may also be influenced by cognitions related to motivation, which is consistent with two studies in the systematic review (Kratz et al., 2011; Osborne et al., 2007) showing that when pwMS felt less inclined to change, or maintain, their persistence with everyday tasks they experienced greater pain interference. Similarly, greater perceived importance relating to task persistence was also correlated with less pain interference, although these correlations were generally small. It may therefore be important to measure cognition and activity avoidance separately to clarify the role of avoidance behaviours. Although fear-avoidance incorporates a combination of cognitive and behavioural elements

(Vlaeyen & Linton, 2000), it was initially placed within the behavioural part of the model in the systematic review. However, it was felt that fear-avoidance reflected a more cognitive and affective construct, rather than a specific behaviour, and therefore has been moved to the cognitive part of the model.

Third, it was also felt that cognitive fusion might be a different way of looking at fear-avoidance in MS pain. However, unlike traditional CBT factors, thoughts and behaviours in ACT are not conceived as separate entities. Cognitive fusion does not specify the nature of a thought, but rather attempts to capture a broader process (or response class) that integrates cognition and behaviour. Cognitive fusion occurs when an individual's behaviour is "caught up" in or dominated by their thoughts or mental images to the extent that they fail to come into contact with other (non-verbal or other cognitive) contingencies in their immediate environment. For example, an individual might be fused with the belief that "exercising when in pain may worsen MS", which may lead to avoidance of physical activity. Over time this may result in further deconditioning, and the person may rarely experience the positive reinforcing effects of taking gentle exercise.

Therefore, it was felt that exploring the potentially protective role of pain acceptance, and potentially unhelpful role of pain-related avoidance-endurance, avoidance of physical and social activities (which do not include a component of fear), and cognitive fusion, in relation to pain severity and pain interference would determine which behavioural responses were most important. MS studies investigating these responses have mostly used small samples. Therefore, examining these behavioural responses within a larger cross-sectional study would allow us to clarify the mixed findings observed in the review and qualitative findings. It was the first study to examine the role of cognitive fusion and avoidance of physical and social activities in the context of MS pain, which may elucidate new avenues for intervention development in the future. For example, it may be that helping pwMS to step back from their pain-related beliefs, by using exercises from ACT or mindfulness treatments, corresponds with shifts in cognitive fusion and acceptance processes, lessens their influence on potentially unhelpful behavioural responses to the improvement pain outcomes.

The cognitive element of the model initially emphasised the predominant influence of pain catastrophizing and the potentially important role of other pain-related beliefs (i.e.

perceived control, chronicity or disability), in determining pain and related functioning in MS. In accordance with this finding, themes around pwMS' vivid descriptions of pain were thought to be related to either a verbal or visual form of pain catastrophizing. In addition, consistent with Leventhal's CSM framework and the illness perceptions identified in the systematic review (Leventhal et al., 2003), qualitative questioning related to pain-specific beliefs resulted in many pwMS expressing that pain was "unpredictable", had varied "causes", would "worsen" over time and was a sign of further damage or disease progression. Therefore, further examining the potentially important role of pain catastrophizing and pain-related beliefs informed by the CSM, was considered to be a useful line of investigation in the cross-sectional study.

The majority of studies in the review showed medium to large sized correlations between depression and anxiety and pain outcomes. However, few examined specific cognitive and behavioural factors or processes outlined in chronic pain theories in chapter 2. Whilst anxiety and depression reflect broader modifiable treatment targets in traditional CBT in MS (Mohr & Goodkin, 1999; Mohr et al., 2000), it was felt that conceptualising and targeting potentially modifiable pain-specific beliefs and behavioural responses in addition to anxiety and depression may be an optimal approach. It was therefore hypothesised that pain-related disability in MS is not only due to negative mood. Since anxiety and depression were expected to overlap with specific contextual and cognitive behavioural factors or processes in the model, efforts were made to account for their influence in regression analyses to determine if finer-grained mechanisms were important in explaining pain severity and pain interference outcomes.

Finally, the qualitative study offered a better sense of how biological factors may interact with other elements in the model. PwMS felt that pain was usually caught up in, or influenced, by other MS symptoms, which often resulting in "Catch-22" vicious cycles. In addition, pwMS use of pain medications sometimes perpetuated these cycles rather than improved the situation. Another key biological factor that did not appear to influence particular themes was the type of pain pwMS experienced. Whilst one person described the traumatic impact of severe trigeminal neuralgia (including shouting and grinding one's teeth during acute episodes), pwMS often reported experiencing a variety of painful symptoms that appeared to result in common cognitive and behavioural responses. Although findings indicate few differences in psychological responses

between people with neuropathic and non-neuropathic pain in chronic pain populations (McCracken & Yang, 2013), there is currently a lack of evidence exploring potential differences between these groups in MS. This was surprising given that the prevalence of neuropathic pain is generally higher in MS compared to other chronic pain populations (O'Connor et al., 2008). Therefore, the current cross-sectional study further investigated the interactive role of pain and other MS symptoms, and examined potential differences in the way pwMS think, feel, and behave in response to both types of pain.

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5.2 Published article

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Article title: Beyond a physical symptom: The importance of psychosocial factors in Multiple Sclerosis pain.

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Abstract

Background and purpose: Pain affects around two-thirds of people with Multiple Sclerosis (pwMS). Biomedical treatments show limited efficacy. A recently developed cognitive behavioural model of Multiple Sclerosis (MS) pain suggests several psychosocial factors may worsen pain and related disability. The current study investigated whether psychosocial factors drawn from this model explain significant amounts of the variance in pain severity and interference over and above measures of disease severity and pain subtype.

Methods: 612 pwMS experiencing pain completed a UK wide cross-sectional survey including valid and reliable psychometric questionnaires. Hierarchical regressions determined the relative contribution of disease severity and psychosocial factors to predicting pain severity and interference.

Results: All psychosocial factors including distress, negative beliefs about pain and its consequences, and avoidance of activity, were related to pain outcomes, explaining a further 24% and 30% of the variance in pain severity and interference after controlling for demographic and disease variables. Findings were similar for neuropathic and non-neuropathic pain subgroups.

Conclusion: All pwMS reported significant pain and associated disability even though over 90% were taking pain medication. Psychosocial factors identified as important in predicting pain severity and, to a greater extent, pain interference are potentially modifiable and may be important treatment targets for both pain subtypes.

Introduction

Pain affects around 63% of people with Multiple Sclerosis (pwMS) (Foley et al., 2012). MS associated pain is typically classified as either neuropathic or non-neuropathic in origin (O'Connor et al., 2008). Between 5% and 32% of pwMS regard pain as their most severe symptom (O'Connor et al., 2008). Current biomedical treatments demonstrate limited efficacy (Beard et al., 2003) and many pwMS experience uncontrollable pain (Kerns, 2000).

A recent systematic review (Harrison, McCracken, et al., 2015) proposed a cognitive behavioural model of MS pain based on existing pain theories (Hasenbring & Verbunt, 2010; McCracken & Morley, 2014; Vlaeyen & Linton, 2000) and a synthesis of existing empirical MS studies (see Figure 1). The model suggests that whilst disease factors trigger pain, a range of non-disease factors significantly determine its severity, extent and resulting disability. These factors include the individual's cognitive (thinking), emotional, and behavioural responses to pain, and social influences, such as level of social support. A recent qualitative study provided some support for this model by showing that pwMS fear worsening pain, perceive their pain as unpredictable, and interpret it as a sign of damage (Harrison, Bogosian, Silber, McCracken, & Moss-Morris, 2014). Many focus on trying to reduce or control pain, using a variety of strategies often resulting in worsening rather than lessening of pain. Whilst a number of quantitative studies have revealed relationships between some of the identified psychosocial factors in the model, such as depression and catastrophizing about pain (Harrison, McCracken, et al., 2015), few have looked at multiple psychosocial factors conjointly to examine which are most important. In addition, to date certain aspects of the model such as beliefs about controllability of pain, and avoidance have not been looked at in published studies of MS. Consequently, there is no coherent understanding of how psychosocial factors fit together in MS associated pain and how they interact with relevant disease variables. It is also unclear as to whether psychological correlates of pain are the same for neuropathic and non-neuropathic pain. To date most cognitive behavioural models of and treatment for chronic pain are based on musculoskeletal (non-neuropathic) pain groups, and very few have directly compared neuropathic and non-neuropathic pain. Although there is preliminary evidence showing that pain subtypes are unlikely to be different in MS (Harrison, McCracken, et al., 2015), it may be important to explore potential differences within a larger MS sample.

The current study aims to (a) describe the type and severity of pain experienced by pwMS, how interfering pain is in relation to other symptoms, and use of medications to control pain, (b) determine the contribution of several potentially modifiable cognitive, behavioural and emotional factors drawn from our previous MS pain model (see Figure 1) (and described in the methods section) to pain severity and pain interference when controlling for measures of disease severity, and (c) conduct sensitivity analyses to determine the contribution of the cognitive and behavioural variables when negative mood (anxiety and depression) is removed (d) examine potential differences in patterns of regression findings between pwMS with neuropathic and non-neuropathic pain.

<table>
<tr><th colspan="2">Biological (Trigger) Factors</th></tr>
<tr><td colspan="2">Pain of Neuropathic origin (due to a primary lesion or disease of the central nervous system)
Pain of Non-neuropathic origin (due to actual or threatened damage to non-neuronal tissue)
Migraine Headache (with mixed neuropathic and non-neuropathic characteristics)
Non MS-related pain (e.g. due to medication side-effects, or a result of other health conditions)</td></tr>
<tr><td>Social Factors</td><td>Cognitions Processes and Thought Patterns</td></tr>
<tr><td><u>Potentially Helpful</u>
Perceived social support

<u>Potentially Unhelpful</u>
Perceived solicitude</td><td><u>Potentially Helpful</u>
Self-efficacy / Perceived control over pain
Pain acceptance*
Present moment awareness
Perceived social support

<u>Potentially Unhelpful</u>
Pain catastrophizing
Fear-Avoidance
Negative beliefs about identity, control/curability and consequences of MS
Negative beliefs about coherence, chronicity, control/curability and consequences of pain
Thought suppression
Perceived solicitude
Increased Self-focused Attention
Cognitive fusion</td></tr>
<tr><td>Behaviours and Behavioural Processes</td><td>Emotional Factors</td></tr>
<tr><td><u>Potentially Helpful</u>
Pain acceptance*
Committed action

<u>Potentially Unhelpful</u>
Avoidance of social activities
Avoidance of physical activities
Over-exertion</td><td><u>Potentially Unhelpful</u>
Depression
Anxiety/Worry</td></tr>
</table>

The boxes highlighted in grey reflect psychosocial factors considered in relation to self-reported pain severity and pain interference where:
Normal text**:** strong evidence, with many studies conducted with studies consistently supporting this role;
Grey text: weaker evidence, where findings appeared consistent but studies were few;
Bold text: factors that may play an important role in MS and primary chronic pain theories that will be tested in the current study;
Italicised text: factors that may play an important role in primary chronic pain theories but have not been investigated in the current study.
The above factors are assumed to interact with one another rather than be unidirectional.
*Pain acceptance has a significant behavioural component and, therefore, is represented as both a cognitive and behavioural process in our model.

Figure 1: Interacting biopsychosocial factors hypothesised to contribute to the severity and impact of Multiple Sclerosis pain (adapted from Harrison, McCracken, et al., 2015)

Participants and methods

This multicentre cross-sectional survey study was approved by the Queen Square London Research Ethics Committee (13/LO/1429).

612 pwMS experiencing pain completed a nationwide cross-sectional study using valid and reliable psychometric instruments. Participants were recruited from a number of sources, including 15 National Health Service (NHS) outpatient clinics. The study was also advertised on the MS Society website and emailed to members of MS UK Register reporting pain. Of the 759 patients with a neurologist confirmed MS diagnosis approached in NHS clinics, 361 (47.5%) completed the postal or online questionnaire. Fifty-one participants from the MS Society website, and 205 (25.6%) of the 800 participants emailed by the MS UK Register responded. We obtained informed consent and completed questionnaires from 617 participants during the period from December 2013 to July 2014. Those participants who could not speak English were excluded. Nine questionnaires were excluded from the final analyses: Four participants reported no pain, two submitted questionnaires with substantial missing data and three were duplicates.

The questionnaire included demographics, disease severity variables, psychosocial instruments drawn from our MS pain model (Harrison, McCracken, et al., 2015) and qualitative interview study (Harrison et al., 2014), and pain severity and interference outcomes.

Disease Severity Measures

Self-administered Expanded Disability Status Scale (EDSS-S) (Bowen et al., 2001). Because of the length of the EDSS-S questionnaire, the mobility scale of the EDSS-S was used as a shorter proxy measure for level of neurological disability, as reported in other studies (Bowen et al., 2001).

MS subtype was determined using established MS subtype pictorials (Bamer et al., 2007) accompanied by lay descriptions. Years of disease duration, and the level of interference caused by other MS symptoms on a 1 to 10 point numerical rating scale, were also obtained.

Years of pain duration and pain medications were recorded, and degree of pain-relief from these medications was assessed using a 0% to 100% numerical rating scale from the Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994).

The Self-report Leeds Assessment of Neuropathic Signs and Symptoms (S-LANSS) (Bennett, Smith, Torrance, & Potter, 2005) was used to identify patients whose pain is dominated by neuropathic mechanisms. The S-LANSS is designed to differentiate participants with pain of predominantly neuropathic origin and those with nociceptive pain using a case identification cut-off score (≥12). It was selected over the Neuropathic Pain Scale (NPS) (Rog et al., 2007), which although validated in MS provides a continuous measure rather than a categorical cut-off (Bennett et al., 2005; Cruccu et al., 2004; Rog et al., 2007). The S-LANSS positive score demonstrates good convergent validity with neuropathic items of the NPS (Bennett et al., 2005).

Potential psychosocial predictors of pain

Mood

Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) was used to measure self-reported anxiety and depression and has good psychometric properties in the MS population (Skerrett & Moss-Morris, 2006). Higher scores indicate greater levels of psychological distress.

Cognitions processes and thought patterns

Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995) was used to assess the extent to which pwMS magnify or exaggerate the threat value or seriousness of pain sensations. The PCS is a valid and reliable instrument (Rosenstiel & Keefe, 1983). The 13-items reflect rumination, magnification and helplessness, with higher scores reflecting greater pain catastrophizing.

Illness Perceptions Questionnaire-Revised (IPQ-R) (Moss-Morris et al., 2002) was used to measure perceived time-course of MS pain (timeline acute/ chronic and timeline cyclical), consequences, symptoms involved (identity), control or curability and how

understandable pain is (coherence). The IPQ-R demonstrates good psychometric properties in several illness populations, including MS (Moss-Morris et al., 2002).

Cognitive Fusion Questionnaire (CFQ) (Gillanders et al., 2014) assesses the degree to which a person's experience and behaviour is "caught up" in or dominated by their own thoughts. This is similar to assuming thoughts are facts, taking thoughts too seriously, or being unable to see beyond one's own beliefs, such as can happen when a person is distressed and experiencing exaggerated or unrealistic thoughts. Cognitive fusion reflects a dimension in human experience where the actions are strongly influenced by the thoughts they are having. The 7-item scale demonstrates good validity and reliability in the MS population, with higher scores reflecting greater levels of cognitive fusion.

Behaviours and Behavioural processes

Avoidance-Endurance Questionnaire Pain-related Behavioural Responses Scale (AEQ) (Hasenbring et al., 2009) is a valid and reliable scale used to assess pain-related behaviours in response to pain, including avoidance of physical and social activities, and a contrasting endurance response, where people continue with activity despite the pain. Higher scores reflect greater levels of avoidance and endurance behaviours.

Chronic Pain Acceptance Questionnaire (CPAQ-8) (McCracken, Vowles, & Eccleston, 2004) comprises two parts, including activity engagement (doing activities in the presence of pain) and pain willingness (refraining from attempts to control or reduce pain). The CPAQ-8 has shown good validity and reliability in recent studies (Fish, Hogan, Morrison, Stewart, & McGuire, 2013). Higher scores reflect greater acceptance of chronic pain.

Pain outcomes

Brief Pain Inventory Short Form (BPI) (Cleeland & Ryan, 1994). The BPI is a valid and reliable (Osborne, Raichle, et al., 2006) instrument assessing two components, including pain severity and pain interference scales, which are standard primary outcomes in all chronic pain clinical trials (Turk et al., 2003). A pain severity index score is calculated using the mean of four severity ratings, including present pain, pain at its worst, least and average in the last 24 hours. The interference scale has seven life domains,

including general activity, mood, mobility, work, relationships, sleep and enjoyment of life. A pain interference index score reflects the mean of all seven domains. Similar to previous studies (Osborne, Turner, et al., 2006) we used a modified short form of the BPI, and we replaced the interference scale item "walking ability" with "mobility (ability to get around)" to account for problems with ambulation in MS.

Statistical analyses

Bivariate correlations, two-tailed t-tests and ANOVAs were used to examine relationships between pain severity and pain interference outcomes and participant demographic and disease characteristics. Two hierarchical regression analyses were conducted to determine if psychosocial factors drawn from our MS pain model (Harrison, McCracken, et al., 2015) predicted pain severity and pain interference outcomes after controlling for relevant demographic and disease variables, including type of pain. The same regression analyses examined moderation, using all psychosocial variables and pain type interaction terms in the third step to see if the pattern of results observed in the hierarchical regression were similar for pwMS with neuropathic pain compared to those with non-neuropathic pain. Finally, four hierarchical regressions were conducted to examine whether psychosocial factors accounted for a similar amount of variance in pain severity and pain interference outcomes for neuropathic and non-neuropathic pain groups after demographics and disease factors. All statistical analyses were conducted using SPSS Version 22 (IBM Corp., New York).

Power analysis for sample size

An *a priori* power calculation using G*Power version 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007) indicated that a minimum sample size of n=128 would be sufficient to detect a medium R^2 effect size =.15, based on data from a previous studies looking at several psychological constructs (Harrison, McCracken, et al., 2015), with a power =.80 at a two-tailed alpha level = .05. This included twelve psychosocial predictor variables within a multiple linear regression fixed model with R^2 increase after including nine demographic and disease variables.

Results

Table 1 shows the disease and demographic characteristics of the MS pain sample (*n*=608). Participants included 156 men and 452 women. The sample was predominantly middle-aged and white in ethnic background with varied occupational status. Forty-seven percent of participants classified themselves as having relapsing remitting disease, while the remainder were equally divided into secondary and primary progressive disease subtypes.

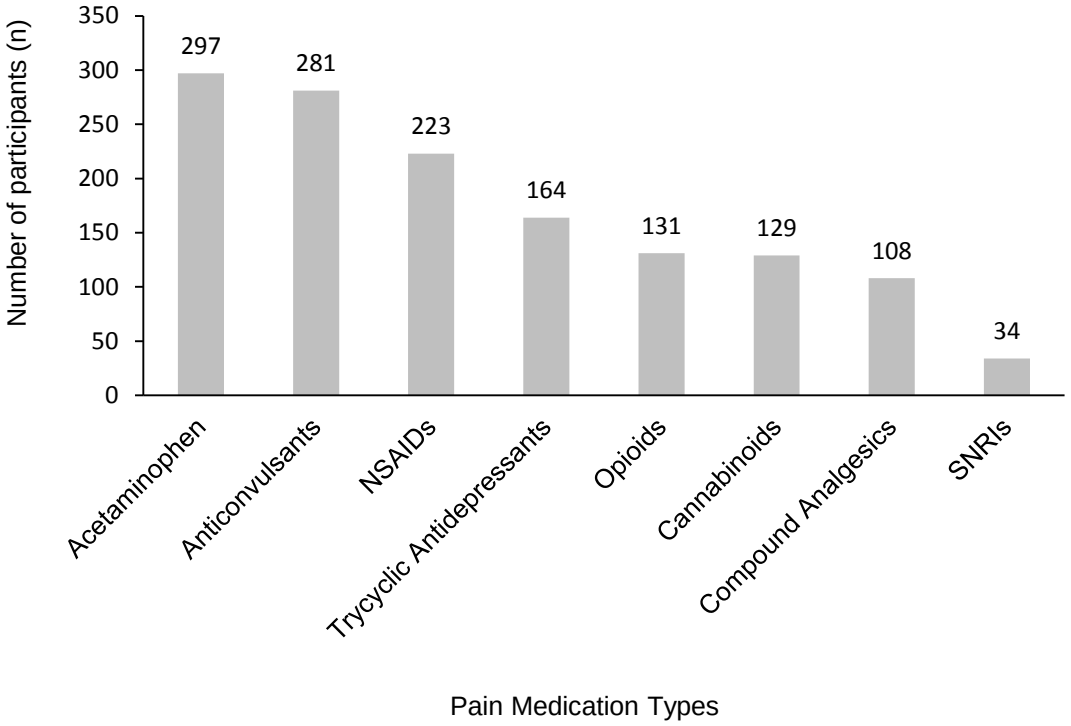
Table 1 MS Sample Characteristics (*n*=604)[a]

Mean Age	52.4 ± 11[b] (95% CIs 51.5 to 53.2)
Gender female *n* (%)	452 (74.3)
Ethnicity white *n* (%)	581 (95)
Unemployed *n* (%)	406 (66.7)
MS subtype pictorials *n* (%)[b]	
RRMS	288 (47.4)
SPMS	158 (26)
PPMS	158 (26)
Mean disease duration years	12.8 ± 9.4 (95% CIs 12.1 to 13.6)
Mean EDSS-S Mobility	5.9 ± 1.3 (95% CIs 5.8 to 6)
Current relapse *n* (%)	99 (16.2)
Relapse not applicable	129 (21.2)
Mean HADS Depression ≥11	15.6 ± 7.0
Pain severity (BPI) (Alschuler et al., 2012b) clinical cut-offs *n* (%):	
0-2 (mild)	92 (15)
3-5 (moderate)	339 (57)
6-10 (severe)	172 (28)

[a]*n* = 604 due to missing data.
[b]Values are mean ± SD
Abbreviations: BPI: Brief Pain Inventory Short Form; EDSS-S: Self-report Expanded Disability Status Scale; MS: multiple sclerosis; HADS: Hospital Anxiety and Depression Scale; PPMS: primary progressive multiple sclerosis RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

On average participants reported a pain severity score of 4.5±2.2[6] (95% CIs[7] 4.3 to 4.6), which according to recognised cut-offs (Alschuler et al., 2012b) reflects pain of moderate severity. Eighty-five percent reported a pain severity score in the moderate and severe ranges. One-hundred and thirty pwMS (27.3%) experienced constant pain, 165 (27.1%) intermittent pain, and 311 (51.1%) both. Five-hundred and eighty six participants (96.3%) reported chronic pain lasting longer than six months in duration (Merskey, 1986). Ninety three percent of participants reported using a variety of pre-defined pain medications (see Figure 2), of which 72% (*n*=409) reported using two or more. On average pwMS indicated that pain medications provided 49.7% ± 29.6 (95% CIs 47.2 to 57.1) of pain relief.

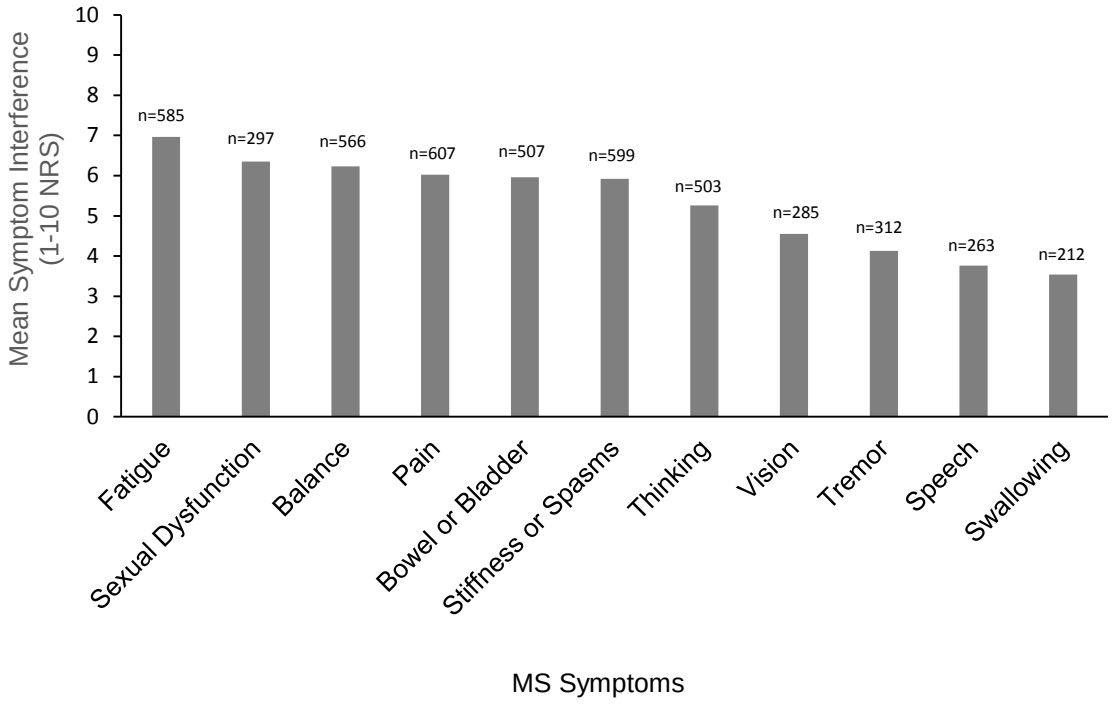
[6] Values are mean ± SD
[7] 95% CIs: 95% Confidence intervals



NSAIDs: Non-steroidal anti-inflammatory drugs; SNRIs: Serotonin–norepinephrine reuptake inhibitors.

Figure 2 Reported Pain Medications

The average pain interference score was 4.8 ± 2.5 (95% CIs 4.6 to 5). Relative to other MS symptoms pain was the most commonly reported and the fourth most interfering symptom (6 ± 2.5 95% CIs 5.8 to 6.2), after fatigue, sexual dysfunction and balance difficulties (see Figure 3). See Table S1 for further correlations between pain and other MS symptoms.



n: number of participants reporting symptom; NRS: symptom interference 1-10 point numerical rating scale using the Brief Pain Inventory (BPI) format.

Figure 3: Frequency of MS symptoms reported and level of interference n: number of participants reporting symptom; NRS: symptom interference 1-10 point numerical rating scale using the Brief Pain Inventory (BPI) format.

The role of psychosocial factors in MS pain severity and pain interference

All psychosocial factors were correlated at the bivariate level with either pain severity or pain interference (see Table 2). Two hierarchical regression analyses were conducted to determine how much variance psychosocial variables accounted for in pain severity and pain interference after controlling for demographic and disease variables (see Table 3). Demographic and disease variables were entered in the first step and psychosocial factors in the second step. The first hierarchical regression showed that demographic and disease variables accounted for 19% ($F=14.63$, $p<.001$) of the variance in pain severity. Psychosocial variables explained a further 24% ($F=19.01$, $p<.001$). Similarly, the second regression demonstrated that demographic and disease variables accounted for 26% ($F=22.29$, $p<.001$) of the variance in pain interference, whilst psychosocial variables explained a further 30% ($F=31.77$, $p<.001$). When removing depression and anxiety from these analyses, the remaining [see thesis Appendix F] cognitive and

behavioural factors still accounted for 23% (F=20.35, p<.000) and 28% (F=31.77=, p<.000) of the variance in pain severity and pain interference respectively. All regression analyses satisfied assumptions of the linear model, including multicollinearity.

Table 2 Psychosocial Correlates of Pain Severity and Pain Interference (BPI)

	Pain Severity (BPI)	**Pain Interference (BPI)**
Anxiety and depression (HADS)	.35** (95% CIs .25 to .41)	.52** (95% CIs .45 to .57)
Pain catastrophizing (PCS)	38** (95% CIs .32 to .43)	.51** (95% CIs .44 to .56)
Pain acceptance (CPAQ)	-.29** (95% CIs -.26 to -.22)	-.50** (95% CIs -.43 to -.55)
Cognitive fusion (CFQ)	.11** (95% CIs .03 to .19)	.31** (95% CIs .23 to .38)
Avoidance-endurance behaviour (AEQ)		
Avoidance of social activities	.23** (95% CIs .16 to .29)	.45** (95% CIs .37 to .50)
Avoidance of physical activities	.19** (95% CIs .12 to .25)	.34* (95% CIs .26 to .40)
Behavioural endurance	.06 (95% CIs -.02 to -.14)	-.09* (95% CIs -.01 to -.16)
Pain perceptions (IPQ-R)		
Time-line	.43** (95% CIs .36 to .49)	.33** (95% CIs .25 to .39)
Time-line-cyclical	-.09* (95% CIs -.01 to -.16)	.03 (95% CIs -.05 to -10)
Consequences	.45** (95% CIs .38 to .51)	.63** (95% CIs .57 to .67)
Personal control	-.22** (95% CIs -.14 to -.29)	-.20** (95% CIs .12 to .27)

Psychosocial predictors: AEQ: Avoidance-Endurance Questionnaire; CFQ: Cognitive Fusion Questionnaire; CPAQ: Chronic Pain Acceptance Questionnaire; IPQ-R: Illness Perceptions Questionnaire; PCS: Pain Catastrophizing Scale
Pain outcomes: BPI: Brief Pain Inventory Short Form.
**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).
95% CIs: 95% Confidence Intervals
n range = 593-607.

Table 3 Psychosocial Predictors of Pain Severity (*n*=567) and Pain Interference (*n*=568) (BPI)

	Pain Severity			Pain Interference		
	Beta	**p**	**ΔR^2**	**Beta**	**p**	**ΔR^2**
Step 1: Demographic and disease variables			.19			.26
			(F=14.63, p<.001)			(F=22.29, p<.001)
			95% CIs			**95% CIs**
Age	-.05	.14	-.13-.02	-.06	.06	-.13-.01
Gender	.05	.12	-.01-.11	.07	.01	.01-.13
Employment status	.03	.33	-.04-.11	.06	.05	-.01-.13
RRMS (Ref) vs SPMS subtype	-.03	.34	-.09-.05	.007	.83	-.07-.09
RRMS (Ref) vs PPMS subtype	-.05	.24	-13-.03	-.001	.98	-.07-.09
No current relapse (Ref) vs Current relapse	.08	.02	<-.01-.16	-.08	.007	-.16-<.01
No current relapse (Ref) vs Not applicable	-.02	.60	-.08-.06	-.05	.10	-.13-.03
Mobility (EDSS-S)	.18	<.001	.09-.25	.19	<.001	.10-.26
Pain type (S-LANSS)	.12	<.001	.03-.20	.05	.05	-.03-.13

BPI: Brief Pain Inventory; Ref: Reference group; Beta: Standardized Coefficients; ΔR^2: R-squared change; Overall R^2: Total effect in regression model; p: 95% significance value; NS: Non-significant parameters; 95% CIs: 95% Confidence Intervals for standardised Beta.
Demographic and disease variables: Employment status: Employed vs unemployed; EDSS-S: Self-report Expanded Disability Status Scale; HADS: Hospital Anxiety and Depression Scale; PPMS: primary progressive multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.
Psychosocial predictors: AEQ: Avoidance-Endurance Questionnaire; CFQ: Cognitive Fusion Questionnaire; CPAQ: Chronic Pain Acceptance Questionnaire; IPQ-R: Illness Perceptions Questionnaire; PCS: Pain Catastrophizing Scale
Pain outcomes: BPI: Brief Pain Inventory Short Form; S-LANSS: Self-report Leeds Assessment of Neuropathic Signs and Symptoms.

Table 3 Psychosocial Predictors of Pain Severity (*n*=567) and Pain Interference (*n*=568) (BPI) Continued

	Pain Interference			**Pain Severity**		
	Beta	**p**	**ΔR^2**	**Beta**	**p**	**ΔR^2**
Step 2: Psychosocial factors			.24			.30
			(F=19.01, p<.001)			(F=31.71, p<.001)
			95% CIs			**95% CIs**
Anxiety and depression (HADS)	.09	.06	-.01-.19	.19	<.001	.10-.28
Cognitive fusion **(**CFQ)	-.14	.002	-.23 to-.05	-.08	.03	-.16-<.01
Pain acceptance **(**CPAQ)	.06	.23	-.04-.17	.01	.76	-.08-.10
Avoidance of social activities (AEQ)	.05	.29	-.04-14	.11	.006	.3-.20
Avoidance of physical activities (AEQ)	-.02	.52	-11-.05	-.01	.74	-.09-.06
Behavioural endurance (AEQ)	.12	.001	.05-.20	.06	.05	.01-.13
Pain catastrophizing (PCS)	.20	<.001	.11-.30	.13	.002	.04-.21
Timeline (IPQ-R)	.24	<.001	.16-.32	.07	.04	.01-.14
Timeline-cyclical (IPQ-R)	-.07	.05	-.13-.01	.01	.54	-.07-.09
Consequences (IPQ-R)	.21	<.001	.11-.30	.35	<.001	.28-.44
Personal control (IPQ-R)	-.05	.14	-12-.01	-.05	.07	-.12-.01
Coherence (IPQ-R)	-.07	.03	-13--.01	-.004	.90	-.05-.05
Step 3: All psychosocial factors and pain type (S-LANSS) interaction terms	NS	NS	NS	NS	NS	NS
		Overall R^2=.43			**Overall R^2** =.56	
		(F=19.57, p<.001)			(F=33.98, p<.001)	

BPI: Brief Pain Inventory; Ref: Reference group; Beta: Standardized Coefficients; ΔR^2: R-squared change; Overall R^2: Total effect in regression model; p: 95% significance value; NS: Non-significant parameters; 95% CIs: 95% Confidence Intervals for standardised Beta.
Demographic and disease variables: Employment status: Employed vs unemployed; EDSS-S: Self-report Expanded Disability Status Scale; HADS: Hospital Anxiety and Depression Scale; PPMS: primary progressive multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.
Psychosocial predictors: AEQ: Avoidance-Endurance Questionnaire; CFQ: Cognitive Fusion Questionnaire; CPAQ: Chronic Pain Acceptance Questionnaire; IPQ-R: Illness Perceptions Questionnaire; PCS: Pain Catastrophizing Scale
Pain outcomes: BPI: Brief Pain Inventory Short Form; S-LANSS: Self-report Leeds Assessment of Neuropathic Signs and Symptoms.

Neuropathic and non-neuropathic pain in MS

Initial t-tests demonstrated pwMS with pain of predominantly neuropathic origin (≥12 on the S-LANSS) reported significantly higher levels of pain severity (t=8.3, p<.001, Mean difference 1.4, 95% CIs 1.07 to 1.74) and pain interference (t=7.0, p<.001, Mean difference 1.4, 95% CIs 1.02 to 1.82), and less pain-relief from pain medications (t=-2.3 p<0.02, Mean difference -5.7, 95% CIs -10.72 to -.83) compared to those with non-neuropathic pain. Our second aim was to conduct moderation analyses by adding psychosocial factors and pain subtype interaction terms as a third step within the first two hierarchical regressions (see Table 3). The interaction step did not significantly explain any additional variance in pain severity or pain interference [see thesis Appendix G], suggesting the pattern of results were similar across the neuropathic and non-neuropathic pain subgroups.

We also conducted separate hierarchical regression analyses for the neuropathic (*n*=342) and non-neuropathic pain subgroups (*n*=225) [see thesis Appendix H and I]. For those with neuropathic pain, demographic and disease variables (including MS subtype, current relapse, EDSS-S gait, and disease duration) accounted for 16% (F=7.72, p<.001) of the variance in pain severity and 27% (F=15.22, p<.001) in pain interference, while psychosocial factors accounted for a further 20% (F=8.32, p<.001) and 25% (F=14.21, p<.001) respectively. For those with non-neuropathic pain, demographic and disease variables accounted for 9% (F=2.75 p=.006) of the variance in pain severity and 15% (F=4.61, p<001) in pain interference, while psychosocial factors accounted for a further 36% (F=11.37, p<.001) and 44% (F=18.16, p<.001) respectively. Together demographic, disease and psychosocial variables explained 8% and 10% more variance in pain severity and pain interference for pwMS reporting non-neuropathic pain compared those with neuropathic pain.

Discussion

This is the largest published study to date specifically investigating pwMS' experiences of pain (Harrison, McCracken, et al., 2015). Consistent with previous MS studies (Ehde et al., 2006; Osborne, Turner, et al., 2006), the current sample of people with MS associated pain showed that 85% of respondents reported clinically significant levels of

moderate to severe pain, whilst 96% reported chronic pain lasting longer than six months. Relative to other MS symptoms pain was the fourth most interfering symptom. Almost all respondents (93%) reported using some form of prescribed pain medication, but on average only achieved 50% of pain-relief when using them. These initial findings suggest that pain is an important problem and biomedical approaches to MS associated pain may benefit from a broader perspective.

In accordance with our biopsychosocial model of MS pain (Harrison, McCracken, et al., 2015) the results indicated that potentially modifiable cognitive, behavioural and emotional factors are likely to play a significant role in the maintenance of increased pain severity and pain interference in MS, accounting for 24% and 30% of the variance respectively, after taking into account relevant demographic and disease variables. The moderate to large effect sizes observed in these multiple regressions are consistent with findings reported in other physical disabilities (Jensen, Moore, et al., 2011) and primary chronic pain conditions (Pincus, Burton, Vogel, & Field, 2002). Sensitivity analyses revealed that even after removing the emotional factor (anxiety and depression) from these analyses the remaining cognitive and behavioural factors still explained a similar amount of the variance in both pain outcomes suggesting that the effects are not just due to negative mood. The bivariate findings suggest all the identified psychosocial factors were associated with pain severity or pain interference, while the regression analyses indicate that certain psychological factors were more pronounced than others after controlling for demographic and disease variables. Specifically, pwMS with higher levels of pain severity and pain interference may have a greater tendency to magnify or exaggerate the threat or seriousness of pain sensations (catastrophic thought processes) and are more affected or influenced by the content of their own thoughts (cognitive fusion, see Gillanders et al., 2014 or McCracken & Morley, 2014 for more in depth discussion of this variable). Greater pain is also associated with a tendency to avoid physical and social activities when in pain, with greater anxiety and depression, and with viewing pain as persistent over time and having serious consequences. It is also worth noting that persisting with activity (endurance) either showed small negative correlations with pain or no relationship suggesting that maintaining activity does not worsen pain whilst avoidance does. Many patients are told by health professionals to rest when in pain and this may in fact not be the best advice.

Predictive models are helpful to quantify relationships between pain, disease and psychosocial variables. However, clearly this is a cross sectional study and causation cannot be inferred. From a clinical perspective, disease factors interact in a reciprocal way with the psychosocial factors. For example, consistent with accounts from our qualitative interview study (Harrison et al., 2014), it may be that pwMS engage in vicious cycles when in pain, where they view pain as always harmful, as having serious consequences or equating to worsening MS. This may result in a struggle to reduce pain by avoiding physical movement and/or social situations, and frequent use of pain medications, even if ineffective or inconsistent in providing adequate pain relief (Beard et al., 2003; Heckman-Stone & Stone, 2001; Kalso et al., 2013). There were also medium to strong-sized correlations between the interference caused by pain and other MS symptoms. Whilst this might suggest that pain and other MS symptoms are correlated and share the same disease process, there is a risk that behavioural efforts employed by pwMS to avoid or reduce pain may also inadvertently exacerbate other MS symptoms. For example, if someone were to rest for long periods because they believed pain was harmful and overused pain medications, this may result in physical disuse and deconditioning, and unpleasant side-effects, which may worsen fatigue, stiffness and spasms. Therefore, certain management choices may increase pwMS' emotional distress and become potentially disabling over time.

Implications for treatment

Our findings suggest it may be helpful to understand and treat MS associated pain drawing from the broader biopsychosocial, patient-centred approaches developed in primary chronic pain. The psychosocial factors identified in the current study reflect specific targets of well-established traditional and contextual cognitive behavioural treatments, which demonstrate good efficacy in primary chronic pain populations (McCracken, 2006; Turk et al., 1983) and when applied to MS fatigue (Knoop et al., 2012). There is also preliminary support for both cognitive behavioural approaches in reducing pain severity and pain interference in MS associated pain (Jensen, Ehde, et al., 2011; Sheppard et al., 2010). However most of these studies are small, uncontrolled and have not been informed by an empirically supported theoretical model of MS associated pain. By defining key therapeutic mechanisms in larger trials, we will be able to refine our conceptual model. In practice, such approaches aim to assist pwMS in identifying

and rectifying potentially unhelpful pain- and treatment-related beliefs and management behaviours that are likely to influence poorer outcome.

Our second aim was to examine potential differences between pwMS with neuropathic and non-neuropathic pain and explore patterns of hierarchical regression findings between pain subgroups. The pain subgroup analyses demonstrated that pwMS with neuropathic pain reported significantly higher pain severity, pain interference and lower levels of pain relief from biomedical treatments. However, moderation analyses indicated no significant differences in the pattern of results for the two groups, suggesting the psychosocial correlates are relevant in both types of pain. However subgroup analyses revealed that disease variables explained more variance in pain outcomes for pwMS with neuropathic pain compared to those with non-neuropathic pain. In addition, disease and psychosocial factors together explained slightly less variance in pain outcomes for those with neuropathic pain compared to those with non-neuropathic pain. This finding is largely consistent with two studies in our MS pain review (Harrison, McCracken, et al., 2015), and in other painful conditions (McCracken & Yang, 2013), which indicate few differences in psychological characteristics between pain subtypes. This suggests that while both pain subgroups are likely to benefit from psychosocial interventions, those with non-neuropathic pain may benefit from an intervention with a larger psychosocial component.

Limitations

The cross-sectional nature of this study limits causal interpretation of the relationships between self-reported pain and psychosocial factors. However, based on what we know about primary chronic pain treatments, it is likely we can modify these factors and improve outcomes for pwMS. One limitation is that all disease factors were collected via self-report instruments (including MS subtype, current relapse, EDSS-S gait, disease duration and pain type), which may be susceptible to either exaggeration or under-reporting by participants, where a clinician rating would have provided greater accuracy. Second, the importance of non-significant psychosocial factors within the regression models may also be underestimated due to common-method variance and conceptual overlap with other psychosocial factors. Third, although the sample size was large, response rates were relatively low, which may limit generalisability of findings. Lastly, the measure used to identify neuropathic pain (S-LANSS) (Bennett et al., 2005)

is yet to be validated in the MS population. Therefore, the moderation and subgroup analyses in this study should be considered preliminary. However, the few studies reporting prevalence of neuropathic pain in MS indicate a large range between 28 to 58%, which may reflect the different clinical evaluations used. Despite the limitations, this study reflects the largest MS associated pain sample to date investigating a variety of potentially modifiable psychosocial factors, guided by a clear theoretical model, providing support for new treatment approaches in MS associated pain.

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Table S1: MS Symptom Interference NRS Bivariate Correlations

	Fatigue	Sexual dysfunction	Balance	Bowel & Bladder	Stiffness or spasms	Thinking	Vision	Tremor	Speech	Swallowing
Pain	**.44**** (95% CIs .37-.50)	**.25**** (95% CIs .14-.35)	**.35**** (95% CIs .27-.42)	**-.26**** (95% CIs -.17- to -.33)	**.46**** (95% CIs .39-.52)	**.38**** (95% CIs .30-.45)	**.29**** (95% CIs .18-.39)	**.33**** (95% CIs .22-.42)	**.29**** (95% CIs .17-.39)	**.26**** (95% CIs .13-.38)

NRS: Numerical Rating Scale; 95% CIs: 95% Confidence Intervals
**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).
n range = 212 to 507.

END OF PUBLISHED ARTICLE

Chapter 6 : Development of the self-management psychological intervention for MS pain.

6.1 Chapter overview

The previous chapter reported on a study of cross-sectional associations between contextual and cognitive behavioural variables and pain outcomes in MS. These findings led to further changes in the working theoretical model of MS pain outlined in the systematic review. The updated conceptual model of MS pain is presented in Figure 8.

The review and qualitative study presented contradictory evidence for the role of avoidant behavioural responses in the context of MS pain. Low quality studies in the review indicated that fear-avoidance shared small or non-significant associations with pain severity and pain interference, whilst qualitative themes indicated that pwMS tended to rest in response to pain and were concerned that over-exerting would lead to worsening pain or disease progression in some cases. The cross-sectional findings examined more specific forms of behavioural avoidance, which offered further support for the idea that pwMS' avoidance of physical movement and social activities in response to pain may result in greater pain severity and pain interference. However, pwMS' tendency to endure with activities in response to pain appeared less important, indicating that greater avoidance-endurance responding may be neither helpful nor unhelpful in the context of MS. Therefore, the model was refined in two ways. First, rather than including fear-avoidance as a potentially unhelpful behaviour (which includes both a cognitive and affective component), avoidance of social and physical activity were incorporated to reflect the cross-sectional data. Second, the 'potentially unhelpful' nature of over-exertion was de-emphasised in the model as there was only a very small but positive effect between endurance behaviours and pain interference. In the context of MS, it appears that endurance behaviours may be neither helpful nor unhelpful in relation to pain outcomes.

The cognitive elements of the model were also updated. Consistent with findings in the review, pain catastrophizing was once again a strong predictor of both pain outcomes and was retained in the model. The distinction between verbal- and imagery-based

catastrophic patterns of thinking, observed in our qualitative study, was not examined because no validated instruments had been developed in chronic pain to assess these differences. Therefore, this remains a gap in our knowledge. The cross-sectional study was the first published study with a large sample to confirm the potentially protective role of pain acceptance. In addition, the earlier qualitative accounts relating to pwMS' pain beliefs were also confirmed to some extent. Perceived consequences and chronicity of pain were strongly correlated with pain outcomes, but perceived control appeared to show only small effect sizes. This finding was less consistent with the pain-related self-efficacy measures used in the systematic review. Similarly, cognitive fusion demonstrated small to medium associations with pain outcomes, which was surprising given that this process appeared to share some conceptual overlap with both unhelpful catastrophic thinking patterns and other pain-related beliefs, and behavioural avoidance.

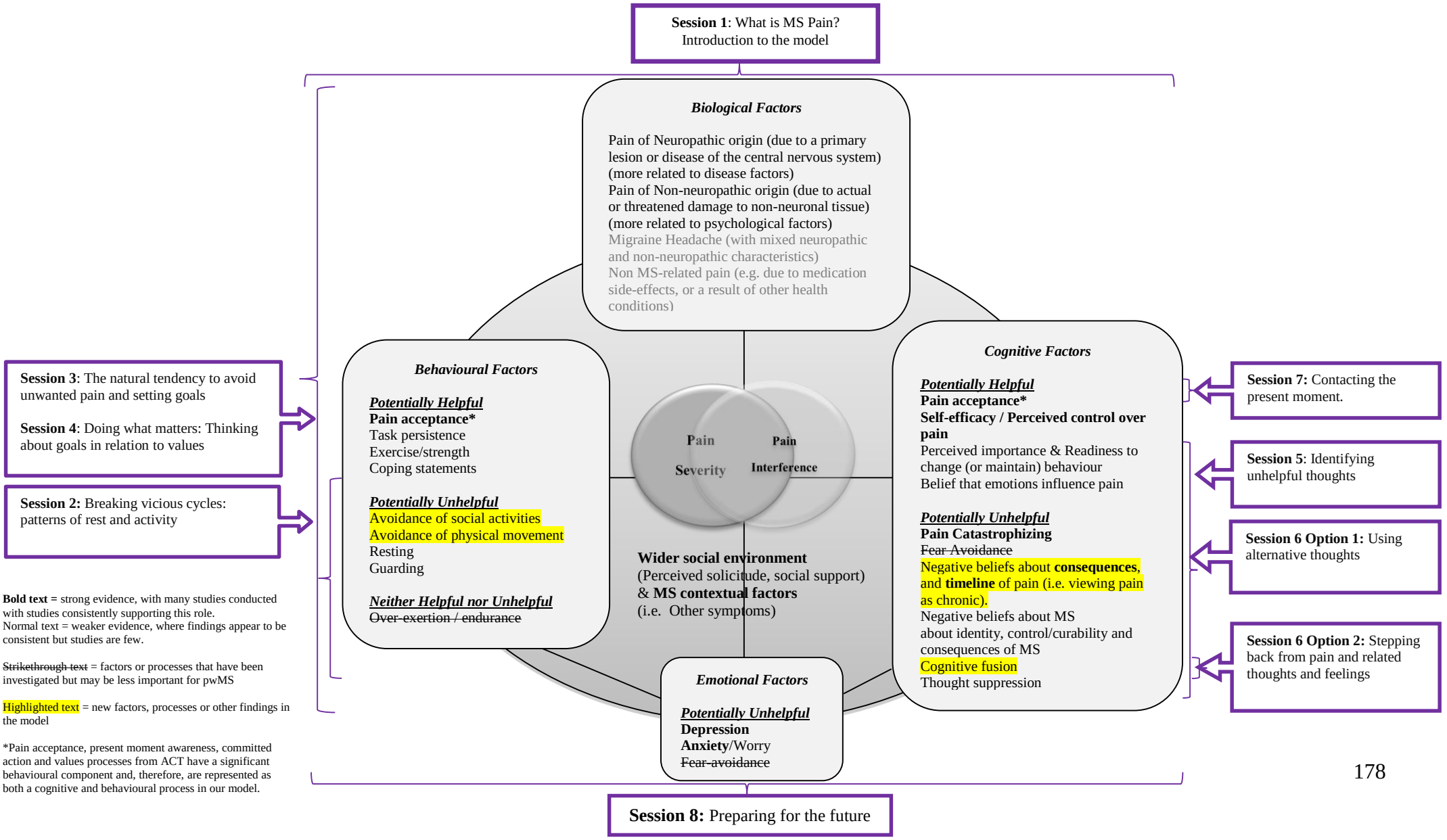
In line with the systematic review and qualitative data, the cross-sectional study provided further confirmation that the different cognitive, behavioural or emotional correlates of neuropathic and non-neuropathic are similar, although disease factors appears to play a stronger role in neuropathic pain. This suggested that both groups were likely to benefit from a contextual or cognitive behavioural intervention that targeted elements within the model, but that effects may be stronger for non-neuropathic pain. In addition, consistent with recent MS studies (Day et al., 2015; Shahrbanian et al., 2015), the significant correlations between pain and other symptom interference ratings in the cross-sectional study to some extent supported the qualitative findings that pwMS may engage in "Catch-22" vicious cycles, where pain and an individual's responses appear to interact with other MS symptoms in a reciprocal way.

In summary, the refined model proposes that whilst disease factors trigger pain, a range of cognitive, emotional and behavioural responses may worsen its severity and interfere with daily functioning. Specifically, pwMS with greater pain severity and pain interference tend to view pain as serious, struggle in their attempts to control or reduce it, can be overwhelmed by their pain, and may avoid physical movement and social activities. In addition, those who experience stronger negative emotional reactions to pain, and have thoughts around pain being chronic, uncontrollable, and as having serious consequences, also report poorer outcomes. It is hypothesised that these psychological processes interact with pain in a reciprocal way, forming vicious cycles that worsen disability over time.

Although the cross-sectional findings suggest that several psychological factors or processes may be important in explaining pain severity and pain interference outcomes in MS, the study design could not explore temporal hypotheses, or determine whether changes in key psychosocial variables preceded changes in pain outcomes over time. An important recommendation of the systematic review was that more longitudinal investigations of change within the context of treatment trials would help to elucidate temporal relationships between potentially important psychological factors or processes and pain outcomes.

The current chapter will therefore describe the development of a cognitive behavioural treatment manual informed by the MS pain model. This was developed with the aim of evaluating the intervention to further test the model. First, a rationale for the self-management treatment approach adopted is provided, and the aims of the programme are specified. This is followed by a short summary of the aims and content of the eight treatment sessions, and how they link back to the working theoretical model of MS pain in Figure 8. The role of the expert research team and MS Society patient and public involvement members (PPI) in providing feedback for the treatment manual are also described. A few examples of revisions to the treatment manual in response to this feedback are outlined. The current chapter closes with a brief conclusion, leading into chapter 7, which evaluates the potential efficacy of the intervention across individuals with both different types of MS and pain.

Figure 8: Updated conceptual model of MS pain and treatment sessions targeting factors or processes (modified diagram Harrison, McCracken, et al., 2015)



Bold text = strong evidence, with many studies conducted with studies consistently supporting this role.
Normal text = weaker evidence, where findings appear to be consistent but studies are few.

~~Strikethrough text~~ = factors or processes that have been investigated but may be less important for pwMS

Highlighted text = new factors, processes or other findings in the model

*Pain acceptance, present moment awareness, committed action and values processes from ACT have a significant behavioural component and, therefore, are represented as both a cognitive and behavioural process in our model.

As mentioned in chapter 2, many of the psychosocial factors and processes identified in our MS pain model (Harrison, Silber, McCracken, & Moss-Morris, 2015) have been shown to be potentially modified in the context of well-established CBT and ACT approaches for primary chronic pain conditions (Veehof, Oskam, Schruers, et al., 2011; Williams et al., 2013) and MS fatigue (Knoop et al., 2012; Moss-Morris et al., 2012; van Kessel et al., 2008; van Kessel et al., 2015).

To date only three pilot studies (Garinger, 2007; Jensen, Ehde, et al., 2011; Sheppard et al., 2010) and one RCT (Ehde, Elzea, et al., 2015) have evaluated cognitive behavioural interventions designed specifically to help pwMS better manage painful symptoms. Of these studies one indicated that a 10 week CBT group programme significantly reduced emotional distress at follow-up, but there were no clinically or statistically significant reductions in pain severity (Garinger, 2007). Another demonstrated that self-hypnosis was superior to cognitive-restructuring training (a key component of CBT), but that a combination of both components was most effective in reducing pain severity and pain catastrophizing, defined as the extent to which pwMS magnify or exaggerate the threat or seriousness of pain sensations (Sullivan et al., 1995), from baseline to post-treatment (Jensen, Ehde, et al., 2011).

The only RCT was published shortly after completing our case-series intervention study outlined in chapter 7. This large single-blinded RCT evaluated the efficacy of an eight week (eight 1 hour session) telephone-delivered CBT self-management treatment (n = 75) to reduce fatigue impact, pain interference, and depression, compared to a telephone delivered education intervention (n = 88) (Ehde, Elzea, et al., 2015). The authors compared the response rate (%) of those pwMS who achieved a reduction in any one of the three target symptoms between the groups. A responder was someone who achieved a >50% reduction in one or more of the target symptoms. Both groups improved in one or more target symptoms at post-treatment. Specifically, the CBT group achieved a 58% response rate, whilst the education group was 48%. Whilst both groups showed significant improvements from baseline to treatment, which were maintained at 12 months follow up, the difference between the groups was not statistically significant. Within-group comparisons showed both interventions resulted in statistically significant reductions in fatigue impact, pain interference, and depression, but effects were generally small for pain interference. In addition, pain severity did not significantly change within the CBT treatment group, but did increase slightly at follow-up. In

contrast, significant reductions were observed in the education group at 6 and 12 months.

Finally, one study evaluated a short five hour workshop based on ACT for *n* = 15 pwMS (Sheppard et al., 2010). ACT and CBT are described in more detail in chapter 2. The workshop showed significant improvements in pain interference and QoL, along with reductions in depression and pain-related thought suppression, at 3 months follow-up. Together these studies indicate that either CBT or ACT treatments may help pwMS better manage pain, and potentially lead to reductions in pain severity and pain interference. Only three of the studies examined psychological variables, including pain catastrophizing and thought suppression, self-efficacy, resilience and negative affect or depression, which improved in conjunction with pain outcomes (Ehde, Elzea, et al., 2015; Jensen, Ehde, et al., 2011; Sheppard et al., 2010). However, none of these treatments were based on a clear conceptual model of MS pain, and other potentially important contextual and cognitive behavioural factors or processes identified within the previous empirical chapters were not investigated.

Traditionally researchers have evaluated CBT or ACT approaches, and their dominant underlying theories, independently. However, previous empirical studies in this thesis indicate that variables from both models explain important variance in pain outcomes, and it is not clear whether CBT or ACT would be more or less helpful. One study in primary chronic pain has examined the potential efficacy of a treatment combining second- and third-wave psychological approaches. This study showed that significant improvements in pain outcomes may be mediated by pain catastrophizing, a key factor identified in the MS pain model (Linton & Fruzzetti, 2014). Therefore, it may be beneficial to evaluate an intervention guided by the MS pain model that combines key elements from both CBT and ACT, which aims to promote pwMS' choice of using techniques from either approach.

6.1.1 Rationale for the development of a self-management intervention

When developing an intervention in the context of MS, consideration of how a treatment may be integrated within current services is important because access to psychological resources is often limited. PwMS may encounter two important barriers when attempting to access current psychological treatments in the UK. First, recent

evidence suggests that pwMS may have limited access to specialist care for symptom management or mental health issues (see MS Society UK, 2015 for full report), which is likely to include access to clinical psychologists and other psychological therapists trained specifically in pain management. Traditionally CBT in the NHS is delivered face-to-face on a one-to-one basis by a highly trained clinical psychologist across 5 to 20 sessions lasting up to one hour (NHS Choices, 2015). However, these therapist-intensive delivery methods may be considered too costly by most health care providers in the current economic context. It is therefore, possible that most pwMS will have limited access to CBT for symptom management. The recent introduction of improving access to psychological therapies (IAPT) (Clark, 2012; Clark et al., 2009) and the role out of this programme for people with long-term conditions means that there will be an increasing workforce of newly trained clinicians with varying levels of psychological expertise who may be available to facilitate this intervention. It may therefore be possible to refer pwMS to low intensity IAPT workers (e.g. assistant psychologists, psychological wellbeing practitioners or primary care mental health workers), who in time may form part integrated care pathways for pwMS. On the other hand, simple, low-intensity psychological interventions could potentially be nurse-led, perhaps with some training, in the context of MS specialist services. A second important issue is that pwMS with greater levels of disability may have difficulty attending sessions due to poor mobility, and may not take into account acute episodes of severe pain or fatigability, cognitive impairment and concentration difficulties (Dennison & Moss-Morris, 2010). Trying to overcome these potential barriers to access may be important to achieve successful implementation of effective treatments in the long-term.

Face-to-face therapy is also a common model of treatment delivery in the broader chronic illness literature. However, in the last fifteen years there has been an increasing shift towards self-management approaches (Barlow, Wright, Sheasby, Turner, & Hainsworth, 2002; Bodenheimer, Lorig, Holman, & Grumbach, 2002; Jovicic, Holroyd-Leduc, & Straus, 2006; Newman, Steed, & Mulligan, 2004; Ramadas, Quek, Chan, & Oldenburg, 2011; Stinson, Wilson, Gill, Yamada, & Holt, 2009), which can either be manual or web-based. One definition of self-management in this literature includes:

"The tasks that individuals must undertake to live with one or more chronic conditions. These tasks include having the confidence to deal with medical management, role

management, and emotional management of their conditions" (Carnes et al., 2012, p. 344).

Most self-management approaches in the chronic illness literature appear to be optimal if they have some support, typically using either telephone or email methods. However, at present there appears to be less evidence indicating what the optimal clinical and cost-effective dosage of support is in the context of psychological interventions for long-term conditions.

In addition to the telephone-delivered intervention for pain outlined in the previous section (Ehde, Elzea, et al., 2015), in the context of MS web- or telephone-based self-management interventions have been introduced as one way to address the problem of cost and availability of CBT. They offer greater flexibility when tailoring treatment content and sessions to varying levels of need and disability. One review of 39 MS studies suggests that telephone- or internet-delivered self-management interventions, including CBT, may improve clinical outcomes, quality of life, and reduce health care costs (Rae-Grant et al., 2011). This is consistent with a more recent review suggesting there is growing evidence for the effectiveness of psychological interventions to improve pwMS' management of several symptoms using a variety of delivery methods (Pagnini et al., 2014). Of the 22 studies in this review, one of the largest treatment effects was demonstrated by a study aiming to improve pwMS' management of fatigue using a face-to-face and telephone supported eight week CBT intervention reviewed in chapter 1 (van Kessel et al., 2008). Two small pilot studies have subsequently tested a web based version of this intervention, where one used minimal telephone and the other email support (Moss-Morris et al., 2012; van Kessel et al., 2015). Both of these low intensity interventions were efficacious, although improvements in fatigue and related interference are unlikely to be as large as those observed using high-intensity face-to-face delivery methods. However, it is difficult to disentangle effectiveness of treatment content from intensity, because studies have used different comparison groups, ranging from treatment as usual (which in many cases may be no treatment at all) to interventions attempting to control for non-specific therapist effects. One way to separate the effectiveness of treatment content from intensity would be to directly compare high- and low-intensity delivery methods in the context of future trials.

There is also a growing body of evidence for self-management psychological interventions in the context of chronic pain. Recommendations from a recent review evaluating the delivery methods of 46 RCTs (of which 38 were psychological interventions) indicate that self-management interventions lasting for less than eight weeks may be an optimal approach (Carnes et al., 2012). However, at present there are no published studies investigating the efficacy of a more time limited self-management intervention based on a combination of CBT and ACT approaches for MS pain using these alternative delivery methods. Therefore, developing a low-intensity telephone supported self-management intervention for MS pain may be a pragmatic approach in the current context. Specifically, for the purposes of this preliminary treatment trial, it was felt that using a detailed self-management manual alongside three one hour treatment sessions offered via telephone or Skype, with a therapist who has a limited amount of training and is not a qualified clinician, may be more realistic in terms of achieving long-term implementation.

6.1.2 Aims of the current self-management intervention

Our main aim was to develop a treatment manual that maps sessions directly onto relevant aspects of the newly developed model. The titles of each session, and which part of the model they most relate to, are mapped onto the model in Figure 8. Although most of the sessions focused on cognitive or behavioural aspects of the model, it is assumed that changes in these will also directly impact on negative emotions. The details of each session are described in Table 2 below. Given the similar pattern of findings for pwMS with different type of pain identified in the systematic review and cross-sectional study (Harrison, McCracken, et al., 2015; Harrison, Silber, et al., 2015), the intervention was designed to broadly target pwMS with neuropathic and non-neuropathic pain.

Consistent with guidance in the chronic pain literature (Turk et al., 2003), the current intervention was designed specifically to target psychological factors or processes within our MS pain model to (a) improve pwMS' engagement in everyday, or other meaningful, life activities by reducing pain interference, (b) reduce their levels of pain severity, and (c) help pwMS to learn and retain a new set of self-management skills, or strategies, to manage pain and assist them in the future. Currently there is insufficient evidence to support the efficacy of biomedical treatments (Beard et al., 2003; De Santi

& Annunziata, 2012; Jawahar et al., 2013), although some pwMS report some benefit from using pain medications (Ehde, Alschuler, et al., 2015; Harrison, Silber, et al., 2015). Therefore, the current programme was designed to be supplementary to biomedical treatments in order to promote choice for pwMS. The programme was designed to be delivered alongside biomedical treatment if it was being received. This meant that participation in the programme did not require that pwMS either to reduce or stop taking altogether their current pain medications.

6.1.3 Overview of eight session treatment manual

Treatment sessions included a range of didactic, experiential, skills training, and educational elements, using materials adapted for pwMS from CBT and ACT interventions in chronic pain (McCracken, 2006; Otis, 2007; Thorn, 2004) and MS fatigue (van Kessel et al., 2008). Aspects of transdiagnostic treatment manuals combining CBT and ACT approaches were also included (Harris, 2009; McKay, Fanning, & Ona, 2011). The manual was developed by the author of the thesis and incorporated feedback from his supervisors and three MS Society PPI members on the usability, usefulness and acceptability of information (this is process is described in more detail in section 6.1.4). The "Guided cognitive behavioural self-management Treatment for MS pain (GIFT)" manual included eight weekly modules summarised in Table 2. All sessions were designed to be interactive and tailored to the individual, including self-assessments, a separate task sheets booklet, and a CD with optional audio exercises. Optional exercises throughout the manual allowed participants to focus on aspects which they felt were more relevant to them, and ignore those which were less relevant. Each session also included homework tasks within the task sheets booklet, which were designed to be completed over the following week and reviewed in the next session. The protocol for the use of the manual included only minimal therapist contact. PwMS received three telephone or Skype sessions throughout the eight week programme, each lasting up to one hour. The telephone sessions were scheduled so that the first one took place after participants completed session 1 to review this chapter (week 2); the second after session 4 to review chapters 2 to 4 (week 4); and the third after session 7 to review sessions 5 to 8 (week 7). All telephone sessions were collaborative in style, using Socratic questioning, guided discovery and validation wherever possible.

Two treatment models were outlined in section 6.1.1, which would either involve support from low-intensity IAPT therapists or MS nurses. To date no studies have directly compared the efficacy of CBT treatments delivered by other health professionals traditionally employed by MS services, low intensity IAPT therapists and highly trained clinical psychologists (Dennison & Moss-Morris, 2010). Therefore, all telephone sessions were delivered by the author of the current thesis, a third year health psychology PhD student, and previously an assistant psychologist, who has completed some training in both therapeutic approaches. The author's level of clinical expertise is therefore assumed to be comparable to that of an assistant psychologist or low-intensity IAPT therapist receiving appropriate training and supervision. The detailed content of each session will now be summarised in the following section.

Table 2 Outline of the hybrid traditional cognitive and contextual behavioural guided self-help treatment (GiFT) manual

Chapters	**Focus**
1. MS Pain explained	What is Multiple Sclerosis (MS) associated pain? A summary of gate control theory, including physiological explanations of different types of pain. Understanding the biological, cognitive, emotional, social/environmental factors triggers and how these can maintain pain. Developing a personal cognitive behavioural model.
2. Breaking vicious cycles: patterns of rest and activity	Levels of activity, rest, and pain are reviewed in relation to individual's models and / or vicious cycles. Information explains how patterns of rest and activity or over-activity affect the body and pain. The importance of consistency in activity and rest is emphasised, and benefits of moderate physical exercise suggested (activity scheduling and self-monitoring).
3. The natural tendency to avoid unwanted pain and setting goals	The natural tendency to experientially avoid pain and associated thoughts and feelings is discussed, along with acceptance-based metaphors and an optional audio exercise *(Observe, Breathe Open up)*. A workability analysis of behaviour (i.e. short- and long-term consequences) is considered in relation to the person's model and vicious cycles. Setting goals related to either activity or avoidance is suggested, and choosing specific and achievable goals is emphasised.
4. Doing what matters: Thinking about goals in relation to values.	Thinking about underlying motivation by exploring the differences between values and goals. Identifying values, including the optional *Eightieth birthday* exercise, and linking to them to goals. Setting values-based goals.
5. Identifying unhelpful thoughts.	Explanation of how perceptions of events can influence a person's responses to pain. Identifying unhelpful thoughts and feelings and considering common traps or 'errors' in thinking.
6. **Option 1:** Using alternative thoughts	Explanation of how to weighing-up a 'negative' thought and learning how to consider possible alternatives to help with levels of distress and limit unhelpful behaviour.
Option 2: Stepping back from pain and related thoughts and feelings.	The problems with suppressing pain, thoughts and feelings are discussed. Defusion exercises are introduced (*Lemons, lemons, lemons* and *"I notice I'm having the thought that…")* to understand the potential influences of thoughts on behaviour, and to get distance from them without trying to change them.
7. Contacting the present moment.	An explanation of the importance of getting present in order to be more open to pain and to pursue values-based goals. Mindfulness exercises are introduced, including audio (*Body Scan*).
8. Preparing for the future.	Developing a future management plan and setting long-term values-based goals with smaller objectives. Exploring potential barriers and identifying physical or emotional warning signs of relapse and normalizing these. Thinking about reconnecting with values and trying again to keep a commitment, or part of a commitment, to values-based goals. Emphasis on continuing to employ the skills learnt throughout the manual to manage their pain.

6.1.3.1 Session 1: MS Pain explained

The aim of session 1 was to engage pwMS in a behavioural intervention by helping them to develop (a) a biopsychosocial understanding of MS pain, and (b) create a personal five-part cognitive behavioural model of MS pain, which provided a rationale for treatment. The review and previous empirical studies indicated that several factors or processes are involved in MS pain. Therefore, psycho-education provided a rationale to help pwMS understand the potentially reciprocal relationship between all aspects of the model that may contribute to, and maintain, pain. This included a detailed summary of the role of potentially important biological, behavioural, cognitive, emotional and environmental factors or processes. A dominant theme in the qualitative study was that pwMS generally felt that pain was difficult to understand or describe. Therefore, to improve their understanding session 1 firstly provided detailed information about the biological aspects of pain, including the different types of painful symptoms in MS and possible causes (e.g. lesions from demyelination or gait problems). The S-LANSS instrument (Bennett et al., 2005) was inserted to help pwMS determine whether their pain was either neuropathic or non-neuropathic in nature, which allowed them to refer to more relevant sections in the chapter and ignore those that were less relevant. In addition, a lay explanation of chronic pain and gate control theory was provided, which emphasised the cyclical relationship between pain and stress (Otis, 2007). Given that many pwMS reported using pain medication even when they were ineffective in the cross-sectional and qualitative studies, a brief section describing the evidence of pain medication in MS, their potential side-effects and consequences of over-use were also outlined.

When introducing the importance of other elements of the model, many explanations of how cognitive, emotional, behavioural and social factors influenced pain were supported by illustrative quotations of pwMS from the qualitative study. The quotations aimed to normalise pwMS' experience of the sometimes challenging situations they may face, including e.g. potentially unhelpful overly solicitous or stigmatising reactions of others. After each element of the model was discussed pwMS were encouraged to complete short interactive self-assessments, which were designed to help them identify some of their own ways of thinking about pain and emotional reactions, and how they and others tend to behave in response to their pain. At the end of the chapter, pwMS

were encouraged to reflect on their self-assessments to create their own personal MS pain model, which explored potential interactions between these key elements. Importantly, the personal model was formulated in collaboration between pwMS and the therapist, where guided discovery was used to ensure the model reflected pwMS' experience. The homework required pwMS to re-read the chapter, or specific sections, in order to consolidate their learning and refine their model in preparation for the next session.

6.1.3.2 Session 2: Breaking vicious cycles: patterns of rest and activity

The primary aim of session 2 was to reinforce pwMS' learning of their personal model by providing detailed examples of how vicious cycles may develop. Some of the examples drew on pwMS "Catch-22" experiences described in the qualitative study. The examples aimed to illustrate in greater detail how vicious cycles can potentially become problematic for pwMS with ranging levels of disability and different life circumstances to engage pwMS. As seen in Figure 8, the qualitative study suggested that pwMS were "careful not to over-exert", "took medications" and engaged a variety a strategies to reduce pain with sometimes limited success. In addition, cross-sectional findings suggested pwMS' may have a tendency to either avoid physical or social activities when experiencing pain, and that enduring with activity when in pain may not necessarily be harmful. Therefore, a particular emphasis in session 2 was placed on unhelpful behaviours in response to pain by describing how patterns of excessive rest and over-activity (in select cases) over the short- and longer-term may affect pain and the body more generally. In addition, the importance of consistency with rest and activity was emphasised, and moderate physical exercise was encouraged. Again, pwMS were asked to complete interactive self-assessments specifically related to patterns of rest and activity and other behavioural responses (e.g. over-using pain medications, alcohol or drugs, or hiding pain from others). PwMS were then encouraged to incorporate these responses and their impact into their personal model from session 1. The session homework required pwMS to use a pain and stress diary to self-monitor their weekly activities, which specifically explored how fluctuating levels of stress and pain may influence each other. The dairy was then reviewed at the start of the following session (forming part of the first telephone session with the therapist) in which Socratic questioning and guided discovery techniques were used.

6.1.3.3 Session 3: The natural tendency to avoid unwanted pain and setting goals

The aim of session 3 was to help pwMS to recognise when they were struggling with pain and related thoughts and feelings when to do so may be potentially unhelpful. Consistent with other studies in the literature (Ehde, Alschuler, et al., 2015; Heckman-Stone & Stone, 2001), a large proportion of pwMS in the cross-sectional study reported using biomedical treatments, but pain-relief appeared to be modest and pain was often persistent. In addition, pain acceptance was related to better pain outcomes in the cross sectional data. The qualitative findings also showed that pwMS had a "pain reduction agenda", reflecting a narrower focus on trying to control or reduce pain even when the short- and long-term effects were not always helpful. One consequence of the pain reduction agenda appeared to be that pwMS' withdrew from engagement in other meaningful life activities. The qualitative study also indicated that pwMS tended to "fight" or struggle with their pain or emotional experience. There was also some evidence in the review to suggest that pwMS had a tendency to suppress their pain-related thoughts. Conversely, pwMS who had a "management and acceptance agenda" appeared to make room for pain in their life and were seemingly less distressed by it. Therefore, session 3 focused on pwMS pain-related behaviours with a particular emphasis on pain acceptance. This session was split into two parts. In part 1 pwMS were introduced to the consequences of experiential avoidance (again, illustrative quotes and examples were used throughout the chapter), and then were asked to examine the workability of their behaviour (i.e. a lay version of a functional analysis). In part 2 participants were then assisted with developing skills in goal-setting.

Part 1: Experiential avoidance (the inverse of pain and general acceptance) in this section was conveyed to pwMS as the natural tendency to avoid unwanted pain, thoughts and feelings. An acceptance metaphor from ACT was used to normalise pwMS' tendency to avoid uncomfortable private experiences ('Quicksand metaphor', see Harris, 2009), aiming to help them understand how avoidance can amplify pain and other problems in the long-term. PwMS were also encouraged to examine the workability of their pain-related behaviours, which involves writing down short- and long-term consequences or "pay-offs" of engaging in a particular behaviour. They were then encouraged to incorporate their findings from the workability analysis into their updated personal model from session 1.

Part 2: PwMS were then encouraged to set workable goals related to issues in their personal model, which were emphasised as an important way to break vicious cycles of pain, or "Catch-22" problems, and related distress. They were asked to set stepped goals to gradually increase meaningful activities (including exercise) in a consistent way. These goals were then monitored closely throughout the programme by the individual and therapist to enhance self-efficacy. The potential link between engaging in goal-directed behaviour and acceptance was also emphasised, where pwMS were asked to complete an optional experiential audio exercise on acceptance ('Observe, Breathe, Open up'). The rationale for acceptance within this exercise was introduced to pwMS as a method to "open up" to their pain sensations, thoughts and feelings to help them engage more fully in meaningful life activities or goals.

6.1.3.4 Session 4: Doing what matters: Thinking about goals in relation to values

Session 4 aimed to help pwMS clarify their values, explore how their current pain-related behaviour may prevent them from acting in the service of their values, and derive personally meaningful values-based goals. Values or committed action have yet to be tested in conjunction with MS pain. However, studies investigating ACT in chronic pain show that values, in combination with acceptance and mindfulness techniques, are associated with reductions in anxiety and may increase motivation, helping individuals to commit to sustainable behaviour change in the long-term (McCracken & Keogh, 2009; McCracken & Velleman, 2010; McCracken & Vowles, 2008). The emphasis on motivation appeared to be consistent with one study in the systematic review, which suggested that motivational elements, such as greater perceived importance of, and readiness to change (or maintain), self-management behaviour, were associated with less pain interference (Kratz et al., 2011). Values were included in the intervention because they seemed particularly relevant for chronic illness populations. Values are not in themselves ends. Rather they can be worked towards, but unlike goals, are never fully achievable. For example, an individual might value "caring for others", which even in the face of serious disease progression, relapse or changes in functioning can still be worked towards in many different ways. Values emphasise flexibility that is sensitive to context. Therefore, an individual might be encouraged to consider a number of values-congruent actions or goals based on their level of disability, ranging from even the smallest gestures of care (e.g. telling someone

they love them or making them a cup of tea) to bigger goals or longer-term projects (e.g. supporting their child with school homework or going on holiday). With the help of fictitious examples, pwMS were encouraged to complete self-assessments, including the forty common values checklist (Harris, 2009) and Values Bull's-eye, which explore the extent of a person's remoteness from their values (Dahl & Lundgren, 2008). An experiential audio exercise ('Eightieth Birthday', see Harris, 2009) was also introduced to help pwMS identify what is ultimately important to them. Homework tasks from this session up until end of treatment asked pwMS to set a number of values-based goals, which were reviewed in each of the following sessions and discussed with the therapist in the second telephone session.

6.1.3.5 Session 5: Identifying unhelpful thoughts

Session 5 aimed to help pwMS identify their thoughts and feelings in response to pain, explaining how both can have a potentially important role in maintaining vicious cycles of pain and distress. CBT has traditionally targeted more general patterns of thinking of the self, world or future related to anxiety and depression, including catastrophic predictions and negative beliefs about coping abilities (Beck, 1991). However, the empirical findings in this thesis repeatedly confirmed the important role of pain-related catastrophic thinking in MS, which may either be verbal or imagery-based in nature. In addition, beliefs around negative consequences, chronicity, and low control of pain to a lesser extent, were also associated with worse pain outcomes. Qualitative themes, including "Pain is unpredictable", "Pain will get worse" / is progressive, and the variety idiosyncratic personal beliefs about the causes of pain also reinforced the idea that pain perceptions informed by Leventhal's CSM model of illness perceptions (Leventhal et al., 1984; Moss-Morris, 2013) played an important role.

Therefore, consistent with a recent CBT intervention for MS fatigue (van Kessel et al., 2008), session 5 targeted both general and pain-specific beliefs. For the latter this meant helping pwMS complete self-assessments to identify pain-related catastrophizing, and appraisals of chronicity, negative consequences (sometimes in conjunction with pain catastrophizing), and potential causes of pain. Illustrative quotes and examples informed by the qualitative study explained how these cognitive events may result in negative emotional responses and potentially unhelpful self-management behaviours. In the second telephone session the therapist also explored appraisals that may be triggered by

acute (e.g. transient unpleasant painful symptoms, or changes in treatment or exercise habits) and chronic health threats (e.g. disease progression, worsening chronic symptoms, loss of function). PwMS were also introduced to common types of thinking errors from traditional CBT to label their pain-specific or general beliefs. In addition, the ACT acceptance metaphor 'Passengers on the Bus' was used to consolidate pwMS' understanding of the process of thought identification and labelling. Along with the self-assessments, pwMS were encouraged to update the thoughts section of their personal five-part model. Finally, pwMS were also introduced to thought records in session 5 with worked examples informed by the qualitative data. Thought records were also used for homework tasks to help pwMS identify situations in which pain-specific, or more general negative beliefs, may lead to potentially helpful or unhelpful behavioural and emotional responses that may worsen pain. They were also asked to label the thoughts according to the common types of thinking list. This work was reviewed in the following session, where again the therapist used a more Socratic style of questioning to continue the collaborative formulation process where guided discovery was encouraged.

6.1.3.6 Session 6: Using alternative thoughts or Stepping back from pain and related thoughts and feelings

The aim of session 6 was to introduce skills to help pwMS better manage their potentially unhelpful pain, or more general negative thoughts, identified in their personal model and previous session. This was with the aim of limiting their influence on potentially unhelpful behaviours outlined in session 2 and 3. Cognitive techniques in traditional CBT suggests individuals unrealistically overestimate negative outcomes, which can result in unhelpful coping behaviours (Beck, Emery, & Greenberg, 1985). Therefore, a combination of thought-challenging and exposure-based methods are commonly used to help individuals overcome anxiety, "enabling them to find more adaptive alternatives in thinking, habituation and de-catastrophization of feared predictions or expectations" (Greer, Park, Prigerson, & Safren, 2010, p. 6). As indicated in our model, pwMS may also monitor and inaccurately interpret painful symptoms as harmful, perhaps as representing worsening disease. However, it was also recognised that pwMS may have realistic fears related to pain and disease exacerbations or progression, and changes in function or treatments. Therefore, in addition to traditional CBT's thought-challenging techniques it was felt an alternative approach might be

helpful to address negative thought patterns specific to MS pain that might be considered 'rational', but which may still be intrusive and distressing. It was also the case that cognitive fusion was significantly associated with pain interference in the cross-sectional study.

Therefore in this session pwMS were given the option to try out (i) thought-challenging (i.e. weighing up a thought and finding useful alternatives) from traditional CBT, or (ii) cognitive defusion exercises from ACT to address unhelpful or distressing thoughts. Defusion and thought challenging methods have divergent aims (Harris, 2009). Thought challenging is primarily interested in modifying the *content* of pain-related thoughts or beliefs and seeking alternatives, whilst defusion exercises focus more on changing the person's relationship to their thinking or *context*, without directly attempting to modify or control thought content. One can therefore defuse from thinking, irrespective of whether a thought it is necessarily 'true' or not (Harris, 2009). More specifically:

In *option 1* pwMS were given worked examples of thought diaries, and were asked a number of key questions to help them weigh-up pain-related or general beliefs identified in their model or previous thought records. The therapist also actively engaged pwMS in this process, sometimes using *in situ* examples, within the second telephone session. This involved asking the individual to provide empirical data on how distressed they were before and after challenging their thinking. In addition, pwMS were reinforced with praise for trying out the task and for testing out different behavioural responses in the presence of thoughts that had previously exerted greater influence over them. They were also encouraged to praise and reward themselves when they tried to do this.

In *option 2* the same process was applied using thought records but instead used ACT's cognitive defusion methods. These included explanatory experiential exercises (e.g. lemons, lemons, lemons) in combination with other techniques, including saying aloud and silently the phrase "I notice I'm having the thought that…" before a potentially unhelpful pain-related, or more general, thought. The rationale for defusion methods were also supplemented by acceptance (e.g. 'Polygraph Metaphor') and paradoxical thought suppression exercises (e.g. 'don't think about a cup of tea'). Homework tasks for both options aimed to reinforce learning by using thought-challenging or defusion exercises as an additional step within weekly thought records.

6.1.3.7 Session 7: Contacting the present moment

Session 7 aimed to teach pwMS present moment awareness or mindfulness skills from ACT. This was described to pwMS as another way to manage pain and related thoughts and feelings when embarking on values-based (i.e. committed) actions or goals. Currently there is no empirical evidence in the MS pain model for associations between pain outcomes and present moment awareness or mindfulness processes. However, a recently identified unpublished study (n = 139) suggests lower levels of mindful awareness is significantly associated with greater pain severity and pain interference in MS (Senders, Yadav, & Shinto, 2014). In addition, a small study evaluating a meditative intervention for pwMS (n = 17) has demonstrated significant reductions in pain severity compared to controls (Tavee, Rensel, Planchon, Butler, & Stone, 2011). Furthermore, a recent pilot study evaluating the efficacy of a Skype distance-delivered eight week mindfulness intervention for MS adjustment has also demonstrated small but significant reductions in pain severity at post-treatment, with moderate improvements observed at three months follow-up (Bogosian et al., 2015). It has also been argued that cognitive defusion in ACT's psychological flexibility model, in combination with present moment awareness and acceptance, are essentially defined as key processes of mindfulness (Hayes et al., 2013). Therefore, this session provided a rationale for improving present moment awareness to help pwMS open up to pain and difficult thoughts and feelings, when to do so allows them to engage more fully in valued activities or goals. In combination with exercises conducted during the third telephone session, several exercises from ACT, including 'Notice Five Things' and three audio exercises ('Leaves on a Stream', 'Tracking Thoughts in Time', 'Free Choice Body Scan'), aimed to help pwMS gain an experiential understanding of mindfulness that could be usefully applied to their everyday routine. A self-assessment was also used to help pwMS identify thinking that may interrupt their attempts to engage in these tasks, which again fed back into their model. PwMS were encouraged to listen and practice those exercises that they found most helpful for five to ten minutes a day. They were also asked to set themselves random reminders on their mobile phones to engage in the exercises to help them notice when they were getting caught up in their thinking.

6.1.3.8 Session 8: Preparing for the future

The final session focused on helping pwMS formulate long-term values-based goals, and related sub-goals, to work towards in the future. Potential barriers or setbacks to achieving goals were also explored in greater detail, and a relapse prevention plan was introduced to help pwMS to anticipate potential problems (e.g. pain flare-ups, exacerbations, disease progression, depression, social issues etc.) to help them manage pain more successfully. Individuals were also encouraged to reflect on newly acquired skills from all previous sessions that might be employed when working towards values-based goals. This session also focuses on ACT's values and committed action processes, despite the fact that neither had been directly tested in the MS pain model. However, other motivational beliefs did appear to be important. PwMS were encouraged to monitor their commitment to values-based goals in a way that normalised the experience of breaking commitments, but also highlighted the cumulative impact of quitting: Including feeling bad about quitting, fearing making commitments, and giving up on making commitments. In contrast, pwMS were encouraged to identify when they break a commitment in the future, and were encouraged to try again to keep the commitment, or part of the commitment. Finally, pwMS were encouraged to change their long-term goals or actions if considered unworkable, and re-clarify their values, particularly if they discover that they are less important to them than initially thought.

6.1.4 Expert feedback and patient and public involvement

The GIFT manual content was developed by the author of this thesis with feedback from his supervisors. His first supervisor, R.M.M., is a qualified registered health psychologist and an expert MS researcher, specialising in cognitive behavioural models of adjustment. His second supervisor, L.M., is a consultant clinical psychologist and lead for a chronic pain inpatient service, and an expert ACT and chronic pain researcher. Several drafts were submitted to both supervisors, who offered feedback on the structure and content of sessions, but also commented on language to promote pwMS understanding of sometimes complex concepts or exercises. For example, behavioural elements of the model were introduced at the start of the programme so as not to alienate pwMS with explanations related to cognition. It was felt that starting with cognitive components may potentially be misinterpreted by pwMS as the research team suggesting that pain is 'not real' or 'all in one's head'. Therefore, this order may

be perceived by pwMS as less stigmatising, aiming to promote better engagement. In addition, terms such as "willingness" and "openness" are used throughout the manual, rather than "acceptance", in order to avoid potentially negative connotations surrounding acceptance equating to resignation or quitting (McCracken, Carson, Eccleston, & Keefe, 2004).

The manual also incorporated a second iteration of revisions. This included feedback from three MS Society PPI members, who were asked via email or telephone to comment on the usability, usefulness and acceptability of information in the programme, and provide suggestions for possible improvements for all eight sessions and associated materials. All three pwMS agreed to participate in several manual and audio exercises and offered experiential feedback. Based on this feedback, and discussions with the research team, a number of adjustments were made to the manual. For example, more fictitious examples of people with progressive MS were included, along with examples of realistic exercise-based goals for wheelchair users in part 1 of session 3. In addition, larger text was used in the manual to assist pwMS with visual problems. Some of audio exercises were re-recorded with simpler and slower instructions to help pwMS with cognitive impairments. In addition, the longer mindfulness exercises were shortened from around 25 to 15 minutes to ensure pwMS with spasticity-related pain and postural difficulties could more easily participate for the full duration.

6.1.5 Conclusions

The current hybrid contextual and cognitive behavioural self-management intervention, based on the MS pain model (Harrison, McCracken, et al., 2015; Harrison, Silber, et al., 2015), aims to reduce pain severity and pain interference in pwMS. One RCT, and a few small pilot, non-randomized and uncontrolled studies have evaluated cognitive behavioural interventions to help pwMS better manage pain. Although promising, the content of these treatment developments were not guided by an empirically supported model of MS pain. In addition, little consideration has been given to limited resources and use of self-management methods. Furthermore, interventions appeared to provide less information about painful syndromes in MS. In contrast, our tailored treatment, informed by our model, targets specific issues related to MS pain, and related biological, cognitive, emotional and behavioural influences. The self-management

methods adopted mean that the GIFT programme has the potential for more pragmatic low-intensity delivery, and could be facilitated by MS specialist nurses or low-intensity therapists, or even be used as a stand-alone self-help resource.

At this stage of development several potential limitations of the GIFT programme were identified. First, the breadth and depth of the programme's content was felt to potentially be too burdensome for pwMS who experience a greater level of disability, cognitive impairment or fatigue. A related issue was that potential burden of the programme was not highlighted by the three PPI members, which might suggest that patient involvement at this stage of development was insufficient. Specifically, all three of the PPI members who contributed to the development of programme were highly educated and motivated individuals from the MS Society. Therefore, in the future it might be helpful to obtain feedback from a wider pool of PPI members from different sources who have varied demographic and disease characteristics. This might go some way to ensure that programme materials are appropriate and accessible for pwMS with a range of difficulties. Despite these limitations, it was felt that one advantage of the self-help format was that it could easily be modified for future roll out, by either reducing or simplifying the content for those pwMS who might experience difficulty in successfully completing the programme in its current form. Given the complexity of some of the content in the GIFT manual, a final important consideration was whether it could actually be delivered reliably by staff with minimal training. It was therefore felt that in the future it might be helpful to develop a brief staff training programme, and competency assessment, which alongside the manual and regular supervision from a clinical or health psychologist, may translate to improvements in therapist adherence to the manual, and fidelity to the model. A future trial could compare delivery by staff with minimal training versus those with high level of expertise to compare the relative clinical and cost-effectiveness of these approaches.

The next chapter will summarise a preliminary investigation into the potential efficacy of the more widely targeted GIFT programme with seven pwMS with a range of demographic and disease characteristics. This evaluation aims to provide useful information about pain outcomes, and targeted psychological factors or processes from the MS pain model, for pwMS with varied types of pain and disease characteristics.

Chapter 7 : A Case-series Study to Evaluate the Potential Efficacy of a Cognitive and Contextual Behavioural Intervention for MS Pain.

7.1 Chapter overview

The current chapter reports on a small, unpublished empirical study investigating the potential efficacy and feasibility of the GIFT intervention for pwMS with different types of pain and a broad range of demographic and disease characteristics. A version of this chapter, incorporating relevant information from chapter 6, has recently been submitted for publication to the *British Journal of Health Psychology*.

Conducting a preliminary evaluation of the GIFT intervention aimed to further revise the treatment and MS pain model. The case series method does not reflect a naturalistic group-based longitudinal design (Barlow & Hersen, 1984). However, it was a useful way to explore how pwMS' pain severity and pain interference change in relation to psychological responses over time in the context of an intervention. Therefore, this study explored temporal relationships between pain outcomes and potentially important contextual and cognitive behavioural mechanisms of change. The current chapter first outlines the aims of the study and provides a brief rationale for the case series method adopted. A more detailed description of methods used to evaluate the GIFT programme is then described. Key findings are then summarised, and the chapter closes with a discussion around theoretical and treatment implications.

7.1.1 Study aims

The purpose of the current study was to investigate the potential efficacy of a telephone-supported hybrid CBT and ACT self-management intervention for pwMS with pain based on our conceptual model (Harrison, McCracken, et al., 2015) using mixed methods. Specific aims were to (a) test the intervention using individual case series to assess potential changes in pain severity and pain interference for a range of pwMS with different demographic and illness characteristics, and (b) evaluate potential psychological processes of change from the model. The systematic review and cross-sectional study (Harrison, McCracken, et al., 2015; Harrison, Silber, et al., 2015) indicated that the strongest psychological correlates of pain severity or pain interference were pain-related catastrophizing, acceptance, perceptions and negative emotional

representations, and avoidance of social activities. Therefore, these processes were specifically targeted in the intervention. The study also aimed to (c) explore pwMS' experiences of the treatment programme within a post-intervention qualitative telephone interview, and (d) inform recommendations for revising and modifying the intervention in the future.

7.1.2 Use of for single-case methodology

Single case series designs provide a quasi-experimental approach to evaluating treatment effectiveness in a single subject or small group of subjects, in which individuals serve as their own controls (Backman & Harris, 1999). Many treatments have been evaluated using more conventional group-based designs, however it has been argued these findings may be misleading because they assume effects at the group level apply to the individual (Weinstein, 2007). Compared to group-based designs the single-case method also allows for a cost-effective investigation of processes of change in psychological interventions (Kazdin, 2011), and provides a more detailed analysis of both "responders" and "non-responders" to treatment (Barlow & Hersen, 1984). Therefore, rather than conducting a group-based pilot trial, a single-case design was used because it allowed us to test how our broadly targeted treatment may work at an individual level for pwMS with a range of demographic and illness characteristics (i.e. disease subtype, level of neurological disability and type of pain). The single case series design was supplemented with qualitative methods to gauge participant's acceptability of the intervention and explore potential processes of change in greater detail to further test the MS pain model.

7.2 Method

7.2.1 Ethical considerations

The study was approved by the Camden & Islington Research Ethics Committee London in December 2014 (14/LO/1909) and informed consent was collected from all participants online or by post.

7.2.2 Design

A replicated single-case time series A-B-A design with a four week baseline, eight week treatment and four week follow-up period, with four-day intervals between assessments, was used to evaluate the potential efficacy of the eight-week telephone-guided hybrid CBT and ACT self-management programme for pwMS.

7.2.3 Recruitment and participants

Participants were selected from a previous UK-wide cross-sectional survey study (*n*=608) (Harrison, Silber, et al., 2015), which recruited pwMS from National Health Service (NHS) MS specialist neurology clinics, and online through the MS UK Register and MS Society. Those participants who expressed a preference to be re-contacted about the current study were mailed an initial invitation letter, information sheet and consent form by the first author. In conjunction with the eligibility criteria below, eleven people were initially invited to take part in the current study based on their demographic and illness data (see Figure 9 CONSORT flow diagram). Specifically, the first author (A.H.) reviewed the available cross-sectional survey data to select potentially eligible participants based on age, gender, ethnicity, MS subtype, level of disability, pain severity and pain interference, pain onset and type of pain. The cross-sectional dataset did not include many younger pwMS, and few were in the early stages of pain onset. Therefore, people with different genders and types of pain were purposefully sampled people with different genders and types of pain, to ensure disease subtypes and varying levels of neurological disability were represented.

7.2.4 Screening and eligibility criteria

Of the eleven participants re-contacted from the previous cross-sectional study (*n*=608) one person had died. Therefore 10 pwMS provided informed consent to complete a brief telephone screening assessment with A.H. The screening assessment included the Telephone Interview for Cognitive Status Modified (TICS-M) (Brandt et al., 1993) where a score of ≥20 was required. The TICS-M is an English modification of a brief standardised ten minute telephone interview procedure that assesses cognitive status. Based on the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), it was originally used to identify cases of dementia, but has been shown to be a helpful tool for identifying people with and without cognitive impairment in studies

where other testing methods are too expensive or impractical (Crooks, Clark, Petitti, Chui, & Chiu, 2005). The assessment comprises 19 items assessing basic cognitive functions affected by dementia, including orientation, concentration, memory, naming, comprehension, calculation, and reasoning. Compared to other brief, in-person neuropsychological examinations, the TICS-M has good interrater reliability, high sensitivity and specificity for the detection of dementia, and is strongly correlated with the MMSE in clinical samples (Brandt et al., 1993). The following eligibility criteria were also assessed during the telephone screen:

Participants were included if they (a) had participated in our previous cross-sectional study, (b) were ≥18-years of age with any subtype of MS, (c) in line with IMMPACT recommendations for all chronic pain trials (Dworkin et al., 2010), experienced pain regularly for at least three months with a current pain severity and pain interference score of at least ≥3 (moderate severity, Alschuler et al., 2012b) assessed using the Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994), and (d) onset of pain needed to have occurred at the time of diagnosis or after a diagnosis of MS.

Participants were excluded if they (a) could not speak and understand English to an acceptable level in order to participate in assessments, reading and telephone sessions, (b) reported previous serious psychological disorders, or (c) showed severe cognitive impairment (≥20 on the TICS-M), or were either (d) starting a new pain medication regimen or (e) psychological therapy for pain during the study period, and (f) had experience of prior formal experience in CBT or ACT approaches.

One person was excluded post-screen because they were expected to start on a new pain medication regimen during the study period, whilst another reported pain related to a bone fracture. The remaining eight participants were sent a confirmation letter asking them to complete an online or paper version of the Self-administered Expanded Disability Status Scale (EDSS-S) (Bowen et al., 2001) to assess their level of neurological disability, MS subtype pictorials (Bamer et al., 2007) and Self-report Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS) (Bennett et al., 2005) to identify any changes in disease variables since the cross-sectional study. The S-LANSS provided a case identification cut-off score (≥12) to identify participants whose pain was dominated by neuropathic mechanisms. The S-LANSS has good convergent validity with neuropathic items of the MS-validated Neuropathic Pain Scale

(Rog et al., 2007). All eight individuals were enrolled on the guided cognitive behavioural self-management treatment programme for MS pain (GIFT) study from December 2014 to May 2015. One participant withdrew from the study due to commitments with full-time education. At the end of the study the seven completers of the programme were given a debriefing statement and £80 to thank them for their participation.

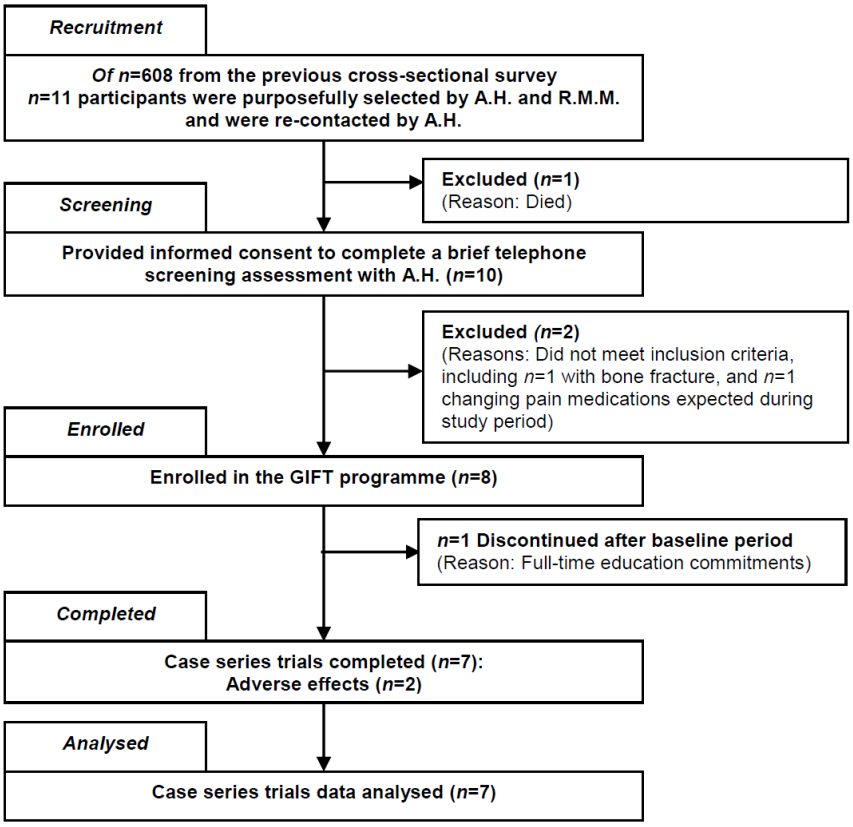


Figure 9: CONSORT diagram participant flow through study

7.2.5 Assessments

All participants completed online valid and reliable self-report instruments assessing pain outcomes and psychological processes every four days during baseline (4 weeks), treatment (8 weeks) and follow-up phases (4 weeks). The four-day interval for ratings, and use of shorter validated instruments, aimed to maximise validity and minimise participant burden. Measures were drawn from our MS pain model (Harrison, McCracken, et al., 2015). All measures demonstrated acceptable internal reliabilities in the previous cross-sectional study (Cronbach's $\alpha \geq .80$) (Harrison, Silber, et al., 2015). Three MS Society UK patient and public involvement (PPI) members assisted with the design of the online ratings, providing feedback on their acceptability and usability.

Every four days during the 16-week period participants were sent e-mail and text message reminders by an independent assessor (K.J.) asking them to complete their online ratings. At 12 weeks participants were invited to take part in a semi-structured qualitative telephone interview with K.J. to explore their experience of the treatment programme (see Appendix N for interview schedule).

7.2.5.1 Primary outcome measures

Brief Pain Inventory Short Form (BPI).

The BPI (Cleeland & Ryan, 1994) is a valid and reliable instrument for pwMS (Osborne, Raichle, et al., 2006) assessing pain severity and pain interference. As part of the four-day ratings, the single-item pain severity 'pain now' scale, ranging from 0 ("no pain") to 10 ("pain as bad as you can imagine"), and a modified 'general' pain interference scale for a given day, ranging from 0 ("does not interfere") to 10 ("completely interferes"), were used. Recent cut-offs specific to MS suggest an average pain severity score of 1 to 2 (mild), 3 to 5 (moderate) and 6 to 10 (severe) (Alschuler et al., 2012b). Guidance in chronic pain suggests that a clinically meaningful change for pain severity reflects a 2-point shift in mean scores, whilst a "substantial change" is 4, and a "minimal change" 1 (Dworkin et al., 2008). The BPI also assesses participant's perceptions of effectiveness of current pain treatments in the last 24 hours, ranging from 0% ("no relief") to 100% ("complete relief").

7.2.5.2 Secondary process measures

Cognitions processes and thought patterns

Pain Catastrophizing Scale (PCS)

The PCS was used to assess the extent to which pwMS magnify or exaggerate the threat or seriousness of pain sensations (Sullivan et al., 1995). The short 13-item scale incorporates rumination, magnification and helplessness, with items ranging from 0 ("not at all") to 4 ("all the time"), with higher scores reflecting greater pain catastrophizing. Scores of >20 indicate elevated risk for problematic recovery warranting further clinical attention (Wideman & Sullivan, 2011).

Brief Illness Perceptions Questionnaire (BIPQ)

Four of the eight items from the BIPQ assessed pwMS' perceived time-course, consequences, control and emotional representations of pain were included. The scale items were modified by replacing the word "illness" with "MS-related pain". Individual items of the BIPQ demonstrate good test–retest reliability and concurrent validity with relevant measures in pwMS (Broadbent, Petrie, Main, & Weinman, 2006).

Behaviours and behavioural processes

Avoidance-Endurance Questionnaire Pain-related Behavioural Responses Scale (AEQ)
The AEQ is a valid and reliable scale used to assess pain-related behaviours in response to chronic pain (Hasenbring et al., 2009). To minimise burden the 6-item avoidance of social activities subscale (ASAS) was selected rather than the avoidance of physical activities subscale (APAS) because it had stronger associations with pain outcomes in our cross-sectional study (Harrison, Silber, et al., 2015). The ASAS usually assesses individual's behaviour in response to both "mild" and "severe" pain, although the subscale was modified to ask pwMS about their avoidance of social activities in response to pain on a given day. Items range from 0 ("never") to 6 ("always") with higher average scores reflecting greater levels of socially avoidant behaviour.

Chronic Pain Acceptance Questionnaire (CPAQ-8)
The CPAQ-8 assesses acceptance of pain, including pain willingness (refraining from attempts to control or reduce pain) and activity engagement (doing activities in the presence of pain). The 8-item scale is a modified version of the CPAQ-20 designed for people with chronic pain (McCracken, Vowles, et al., 2004; Vowles, McCracken, McLeod, & Eccleston, 2008). Each item is rated on a scale ranging from 0 (''never true'') to 6 (''always true''), with higher scores reflecting greater acceptance of pain. The CPAQ-8 demonstrates good validity and reliability in chronic pain populations (Fish et al., 2013; Fish, McGuire, Hogan, Morrison, & Stewart, 2010)

7.2.6 Treatment

The "Guided cognitive behavioural self-management Treatment for MS pain (GIFT)" manual was based on the updated model of MS pain, which was described in detail in the previous chapter. All treatment sessions were delivered by the thesis author, a third year health psychology PhD student who was guided by the content of the treatment

manual and attended training sessions in both approaches. During the treatment phase he was supervised fortnightly by his supervisor R.M.M, a qualified registered health psychologist. Other supervisory specific issues related to treatment methods were discussed conjointly with his second supervisor L.M., a lead consultant clinical psychologist for a chronic pain service in London and specialising in ACT. All sessions were audiotaped for fidelity checking by the fifth author throughout the study and used for supervision.

7.2.7 Statistical analyses

Time series data were plotted and visually inspected for each participant to explore differences in pain outcomes at pre-treatment (phase A), treatment (phase B), and follow-up (phase C). Whilst visual inspection of plots is recommended by experts in the field (Kazdin, 2011; Perone, 1999), recent studies show this method, and use of conventional statistics, can overestimate effects of interventions because time series data is autocorrelated (Borckardt & Nash, 2014; Borckardt et al., 2008). Therefore, Simulation Modelling Analysis (SMA) software Version 8.8.3 (Borckardt & Nash, 2014) was used to generate effect sizes and autocorrelation (*AR*) adjusted p-values related to (a) the mean difference between baseline and intervention phase, and (b) rate of change in ratings from the start of treatment. To explore if changes in pain were maintained, or continued to improve at one month post-treatment, the same analyses compared baseline (phase A) and follow-up ratings (phase C). In the current study 10000 resamples were conducted for each test. Pearson's *r* values were converted to Cohen's *d* to aid interpretation. Whilst other conventional approaches for analysing time series data were considered (see Box & Jenkins, 1970; Crosbie, 1993; McKnight, McKean, & Huitema, 2000; Robey, Schultz, Crawford, & Sinner, 1999), simulations indicate SMA protects against Type I error, whilst providing greater than 80% power to detect effects with 5 to 30 data points per phase (Borckardt et al., 2008).

All secondary psychological variables were visually plotted and the same phase- and slope-effect analyses were conducted using SMA. All valid instruments were scored allowing for 20% of missing data. Missing data was minimal (<0.01% across the sample), and dealt with using a last observation carried forwards imputation method. The distribution for each individual's data was checked to determine whether it met the assumption of approximate normality. This did not indicate any extreme outliers across

participants, which is partly due to the restricted response range of instruments. As such the mean is unlikely to be overly biased as an indicator of central tendency even where the distributions are skewed. Furthermore, whilst the distribution of data streams were platykurtic in some cases, this is likely to result in SMAs tests being more conservative.

Finally, the post-treatment qualitative interview exploring the individual and group perspectives of the programme were analysed by A.H. following established guidelines for inductive thematic analysis. First, key themes were derived for each individual, which were then linked to their quantitative data, and themes common to all participants were then explored. Due to time constraints only A.H. was involved in the process of identifying key individual and group themes. Therefore, coding and thematic developments were not cross-checked by another person. However, K.J. conducted an independent content analysis of all interview transcripts as part of her intercalated BSc project, which was subsequently used to explore similarities and discrepancies with A.H.'s thematic developments.

7.3 Results

Of the seven participants completing treatment, four were recruited from NHS outpatient neurology clinics in the UK, two from the MS UK Register and one from the MS Society. As seen in Table 3, four participants were women and three men, ranging from 37 to 65 years of age, were predominantly White-British, with varied occupational status. There was almost even split of pwMS reporting neuropathic and non-neuropathic pain, and each participant experienced pain of moderate to severe intensity in a variety of locations according to recent cut-offs (Alschuler et al., 2012b), for a substantial amount of time (ranging from 2.5 to 15 years). At initial assessment all pwMS were using at least two pain medications (see Appendix O), reporting varied levels of pain relief from their medications. Whilst there was a variety of disease subtypes, all participants experienced moderate to severe levels disability. Participant's level of neurological disability ranged from being fully ambulatory without aid, despite relatively severe disability, to essentially being restricted to a bed, chair, or wheelchair.

Table 3 Participant characteristics at recruitment

ID	Age	Gender	Ethnicity	Employment Status	MS Subtype[1]	Years Since Diagnosis	Neurological Disability (EDSS-S)	Pain Severity (BPI)[2]	Pain Interference (BPI)	Pain Location	Pain Subtype (S-LANSS)[3]	Pain Duration
1	42	Female	White-British	Retired	RRMS	20.54	6.5	8	7	Right torso, legs, eyes	14 (N)	2.58
2	37	Male	Mixed-White and Asian	Part time	RRMS	8	6	4	4	Hands, Legs	18 (N)	8
3	47	Female	White-British	Full time	RRMS	2.65	4.5	8	8	Feet legs, face	24 (N)	2.58
4	45	Female	White-British	Unemployed	SPMS	23.55	6.5	8	5	Chest, legs, head	11 (NN)	2.91
5	45	Male	White-Scottish	Retired	PPMS	17.53	8	7	7	Feet, legs, hands, face	10 (NN)	14.61
6	65	Male	White-British	Retired	SPMS	19.03	7	4	4	Buttocks, feet, legs, arms	9 (NN)	11.8
7	56	Female	White-British	Unemployed	PPMS	9	7	5	7	Chest, legs, head, neck	19 (N)	8.03

ID: Participant identification number**;**

Disease variables: RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis PPMS: primary progressive multiple sclerosis; EDSS-S: Self-report Expanded Disability Status Scale; S-LANSS: Self-report Leeds Assessment of Neuropathic Signs and Symptoms; N: neuropathic pain; NN: non-neuropathic pain.

Pain outcomes: BPI: Brief Pain Inventory Short Form on entering the study.

[1]Bamer et al's (2007) MS subtype pictorials with lay descriptions.

[2]All participants reported a pain severity score of 3 or greater, which according to recognised cut-offs (Alschuler, Jensen and Ehde, 2012) reflects pain of moderate to severe intensity.

[3]This is an approximation based on a self-report measure not yet validated in the MS population: A score of 12 or greater indicates pain of neuropathic origin (Bennett et al, 2005).

In this section primary pain outcomes are summarised, followed by secondary psychological processes. Qualitative themes for each individual and the wider group are briefly described alongside these findings (see Table 4 for more detail).

7.3.1 Primary effects

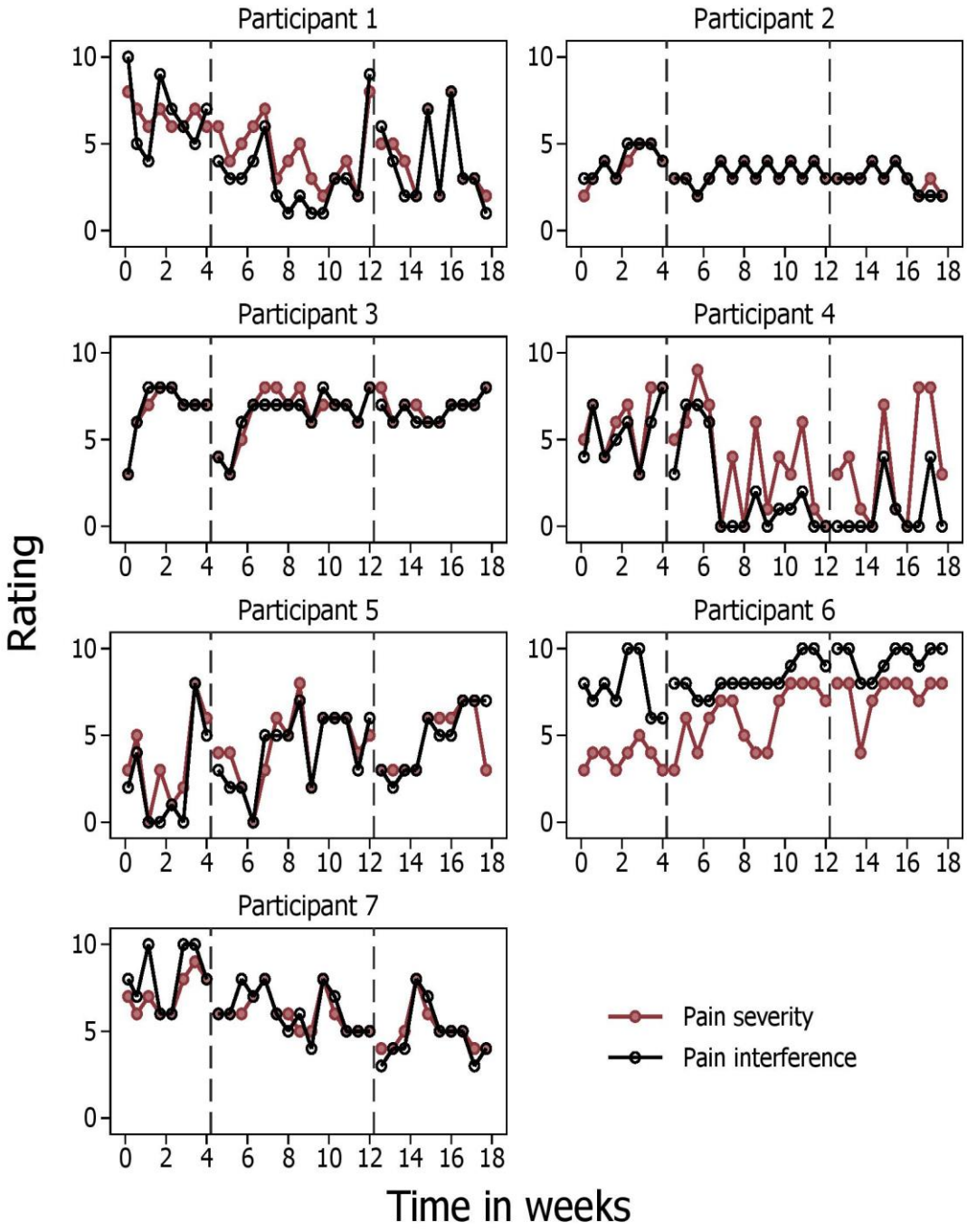


Figure 10: Four-day pain severity and pain interference ratings (0–10) Brief Pain Inventory (BPI) at baseline, treatment, and follow-up for participants 1 to 7

Visual plots presenting four-day pain ratings (BPI) for all participants during the 16 week period are summarised in Figure 10. Whilst qualitative findings suggest that all pwMS felt the programme was *"beneficial"*, individual pain ratings were variable. Three out of seven participants (1, 4 and 7) showed significant improvements in pain severity and pain interference from baseline to treatment, or treatment to follow-up, whilst two pwMS reported unchanging scores (2 and 3), and two got worse (5 and 6). Descriptive statistics, effect-sizes, autocorrelation estimates *(AR)*, and *AR*-adjusted p-values for pain outcomes are presented in Appendix P.1 and P.2. Participant 1 had RRMS with neuropathic pain, reported decreases in both pain outcomes, with a large clinically (see Dworkin et al., 2008) and statistically significant phase change in pain severity ratings from baseline to treatment (Phase A, M = 6.63, Phase B, M = 4.5, d = 1.42, p = .029), and when comparing baseline to follow-up, after controlling for *AR* (Phase A, M = 6.63, Phase C, M = 3.88, d = 1.67, p =.007). A similar finding was identified for pain interference (Phase A, M = 6.63, Phase B, M = 3.38, d = 1.50, p = .030; Phase A, M = 6.63, Phase C, M = 3.50, d = 1.42, p = .013).

Whilst participant 4 showed a clinically significant mean reduction of 2.3 in pain severity across phases, and significant slope change from baseline to treatment (r = -0.54, p = .017), all phase comparisons were not statistically significant. Participant 4 had SPMS and non-neuropathic pain, and decided to reduce her pain and spasticity medications (Gabapentin by 300mg and Baclofen 10mg per day) at the start of treatment (day 36), and moved house on day 64, reporting increased levels of stress related to this activity. She also reported a large 2.5 point mean reduction in pain interference at the onset of treatment after baseline, although this finding was only significant for slope (r = -.77, p=.019) rather than phase change (Phase A, M = 5.38, Phase B, M = 1.81, d = 1.50, p = .100). However, she showed clinically and statistically significant improvements in pain interference when comparing baseline to follow-up ratings (Phase A, M = 5.37, Phase C, M = 1.12, d = 2.58, p =0.003). Similarly, participant 7 had PPMS and neuropathic pain, showing only slope change decreases for pain severity from baseline to treatment (r = 0.81, p = .018) and follow-up (r = -0.74, p = .023). However, she demonstrated large clinically and statistically significant improvements in pain interference from baseline to treatment (Phase A, M = 8.12, Phase B, M = 5.81, d = 1.44, p = .044), which were maintained at follow-up (Phase A, M = 8.12, Phase C, M = 5.12, d = 1.90 p = .029).

Consistent with visual plots, two participants with RRMS and neuropathic pain (2 and 3) did not appear to show any statistically significant improvements in pain severity or pain interference during the 16 weeks. Whilst participant 2 showed a non-significant trend of improvement in pain interference at follow-up (Phase A, *M* = 4.00, Phase C, *M* = 2.88, *d* = 1.35, p = *ns*), participant 3's pain severity and pain interference mean scores were mostly unchanged. This was consistent with participant 2's view that his pain had not improved despite his efforts to change it (see Table 4), whilst participant 3 reported that she did not apply her new skills when experiencing higher levels of pain. Both participants were employed full time, and expressed they found it quite challenging to *"play catch-up"* with the GIFT homework tasks due to work.

Pain outcomes worsened for two cases (5 and 6). Participant 5 showed a non-significant trend of increasing pain severity and interference of around 1 to 2 points respectively. This person had PPMS and was severely disabled, experiencing several health problems during the programme, including severe trigeminal neuralgia. Consequently, his gabapentin was increased from 100mg to 400mg daily in the first few weeks of treatment, and from day 24 this increased to 1200mg over the following six weeks. At the time he and his carer reported that the increase of medication adversely affected his concentration and fatigue, preventing him from absorbing some of the session content in the treatment booklet. At day 84 (follow-up) participant 5 was also prescribed tramadol 50mg daily, and was later hospitalised with Pneumonia during the follow-up period (day 114). His deteriorating health was consistent with his view that examples provided in the booklet were not adequately tailored to his greater levels of physical disability (see Table 4).

Participant 6 had SPMS and severe non-neuropathic pain preventing him for walking. He also reported gradually worsening pain severity (slope change *r* = 0.81, p =.018) and pain interference (*r* = .59, p = .052) from baseline to treatment, demonstrating a large significant increase in pain severity at follow-up (Phase A, *M* = 3.75, Phase C, *M* = 7.25, *d* = 3.40, p = .02). However, he also reported low mood related to feeling socially isolated. At day 66 he contacted the first author to report that he felt increasingly depressed and demotivated, and was bed-bound for two days despite experiencing a period of improvement with graded exercise goals in the previous week. On completing his final telephone session (day 80) he had only completed session 4 of the eight week

programme, and therefore did not attempt any of the cognitive strategies in later sessions. In contrast, all remaining participants completed both optional cognitive modules in the programme booklet.

In some cases SMA produced small, and a few negative, phase and slope *AR* estimates for pain outcomes (see Appendix P.1 and P.2). In discussion with a local statistician (S.N.), and through email correspondence with a cofounder of SMA, it was felt that the design and structure of the data could potentially lead to underestimation of the *AR* in pain outcomes. Low and negative *AR* estimates may be problematic because they can potentially bias the model in favour of finding differences that may not exist (Type I error). More conventional single case series approaches typically analyse a greater number of data points per phase or slope using daily ratings, which may produce more accurate *AR* estimates. Therefore, sample *AR* estimates for pain outcomes were calculated by combining all seven pwMS' data streams using SPSS Version 22 (IBM Corp., New York, NY, USA). This resulted in an overall lag-1 or *AR* =.42 estimate for pain severity, and *AR*=.56 for pain interference.

A sensitivity analysis was then conducted for those phase and slope simulations that indicated statistical significance, but had an *AR*=<.40. A more conservative estimate was achieved by manually imputing *AR* estimates of .40 into SMA simulations for both pain severity and pain interference. The + symbol in Appendix P.1 and P.2 indicates which simulations remained significant at the p=.05 level after these analyses. For pwMS who showed significant phase and slope effects for pain severity with an *AR* = <.40, six sensitivity analyses indicated that when an *AR*=.40 was imputed 50% of effects (3 out of 6) remained significant at the p=.05 level (see Appendices P.1). Similarly, 40% of effects (2 of 5) remained significant when an *AR*=.40 was manually entered for pain interference (see Appendices P.2).

7.3.2 Secondary processes

Five participants reported changes in secondary psychological processes, despite only three showing significant trends of improvement in pain outcomes. First we summarise the three participants who improved (1, 4 and 7), followed by those who did not (2, 3), and those who got worse (5 and 6). The visual plots for the four-day ratings (z-scores) for pain catastrophizing (PCS), pain acceptance (CPAQ-8) and avoidance of social

activities (ASAS) for each participant over the 16-week period are presented in Figure 11, with corresponding SMA outputs in Appendices Q.1 to Q.3. Perceptions and emotional representations of pain (BIPQ) are presented in Figure 12 with statistical tests in Appendices Q.4 to Q.7.

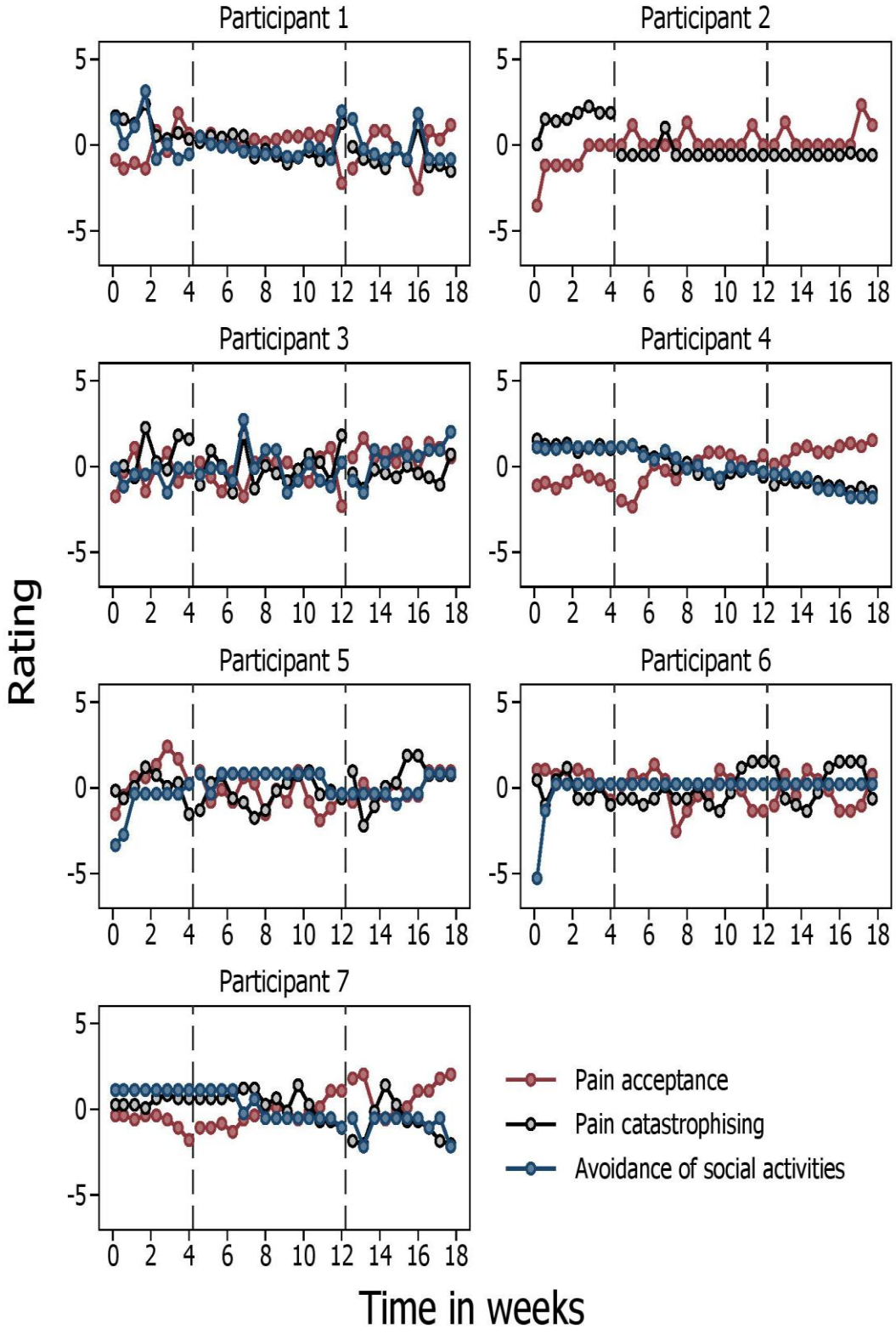


Figure 11: Four-day ratings of Pain Catastrophizing (PCS), Pain Acceptance (CPAQ-8) and Avoidance of Social Activities (AEQ-ASAS) at baseline, treatment, and follow-up for participants 1 to 7 (Z-scores)

Visual plots and analyses for participant 1 show several psychological processes changed in parallel with reductions in pain outcomes. She experienced mostly large significant reductions in pain catastrophizing, negative emotional representations, and perceived consequences and chronicity of pain when comparing baseline to treatment, and baseline to follow-up, ratings after controlling for *AR*. However, participant 1 did not show a statistically significant change in pain acceptance, social avoidance or perceived control. The latter was inconsistent with her qualitative data (see Table 4), where she felt the intervention increased her sense of control over pain. She also treated goals as *"mini projects"*, linking them to her values and self-worth, and found behaviours she practised in the service of goals gradually became a natural part of her routine.

Participant 4 experienced large significant increases in pain acceptance, and large statistically significant reductions in pain catastrophizing, avoidance of social activities, negative emotional representations, and perceived pain as less chronic at follow-up. Consistent with these changes, she described how she learned to pace and prioritise her goals, which resulted in less anger, and mindfulness exercises helped her to *"let go of difficult thoughts and feelings"*. Whilst she reported a non-significant trend towards perceiving more serious consequences of pain from baseline to treatment, this trend reversed at follow-up. She also experienced no change in perceived control.

At follow-up participant 7 showed significant reductions in perceived consequences of pain and avoidance of social activities. She experienced gradual slope reductions in negative emotional representations, perceived chronicity and pain catastrophizing, and an increase in pain acceptance, from baseline to follow-up. This was consistent with her view that mindfulness exercises and writing down thoughts "*stopped her from acting on her thoughts, fears and anxieties"* related to pain, allowing her to focus on goals. She started a new romantic relationship near to the end of the treatment phase, which she suggested in combination with the treatment, increased her confidence to *"lead a more normal life"*. She also experienced no change in perceptions of control.

Whilst participants 2 and 3 did not show significant improvements in pain outcomes, they did report changes in psychological processes. Participant 2 had large significant reductions in pain catastrophizing and negative emotional representations of pain, perceiving pain as less chronic and as having less serious consequences from baseline to

treatment, and at follow-up. This appeared to be consistent with his view that the treatment was mostly about *"changing his attitude"*. Whilst he also showed a statistically significant increase in pain acceptance at follow-up, this is unlikely to reflect a clinically significant change (McCracken, MacKichan, & Eccleston, 2007).

Participant 3 experienced a small reduction in pain catastrophizing, consistent with her view that she no longer "*completely panics"* when experiencing pain (see Table 4). However, whilst she viewed pain as having less serious consequences during treatment, she subsequently perceived pain as more having serious consequences at follow-up. She also viewed her pain as significantly less chronic from baseline to treatment, and increased levels of pain acceptance at follow-up, although these changes were small. Whilst this was consistent with her description of re-engaging in valued activities despite pain, she also reported a significantly greater tendency to avoid social activities at follow-up. Her unchanging negative emotional feelings towards pain was also inconsistent with her view that she was getting less drawn into vicious cycles and experienced a positive change in her *"state of mind"*, although she did report a non-significant 1-point increase in perceived control.

Participant 5 and 6 showed no changes in psychological processes. However, participant 5 felt the programme kept his brain occupied and learnt new distraction techniques. Participant 6 reported experiencing complete control (BIPQ) over his pain throughout the 16 weeks, despite having significantly worse pain outcomes. However, he said he learned *"not to battle with pain"* and was *"less frightened"*, but was also *"shocked"* at how remote from his values he had become (e.g. being creative), suggesting that recurrent physical health problems (i.e. urinary infection) and fear of his partner's disapproval undermined his motivation to work towards valued goals (e.g. painting).

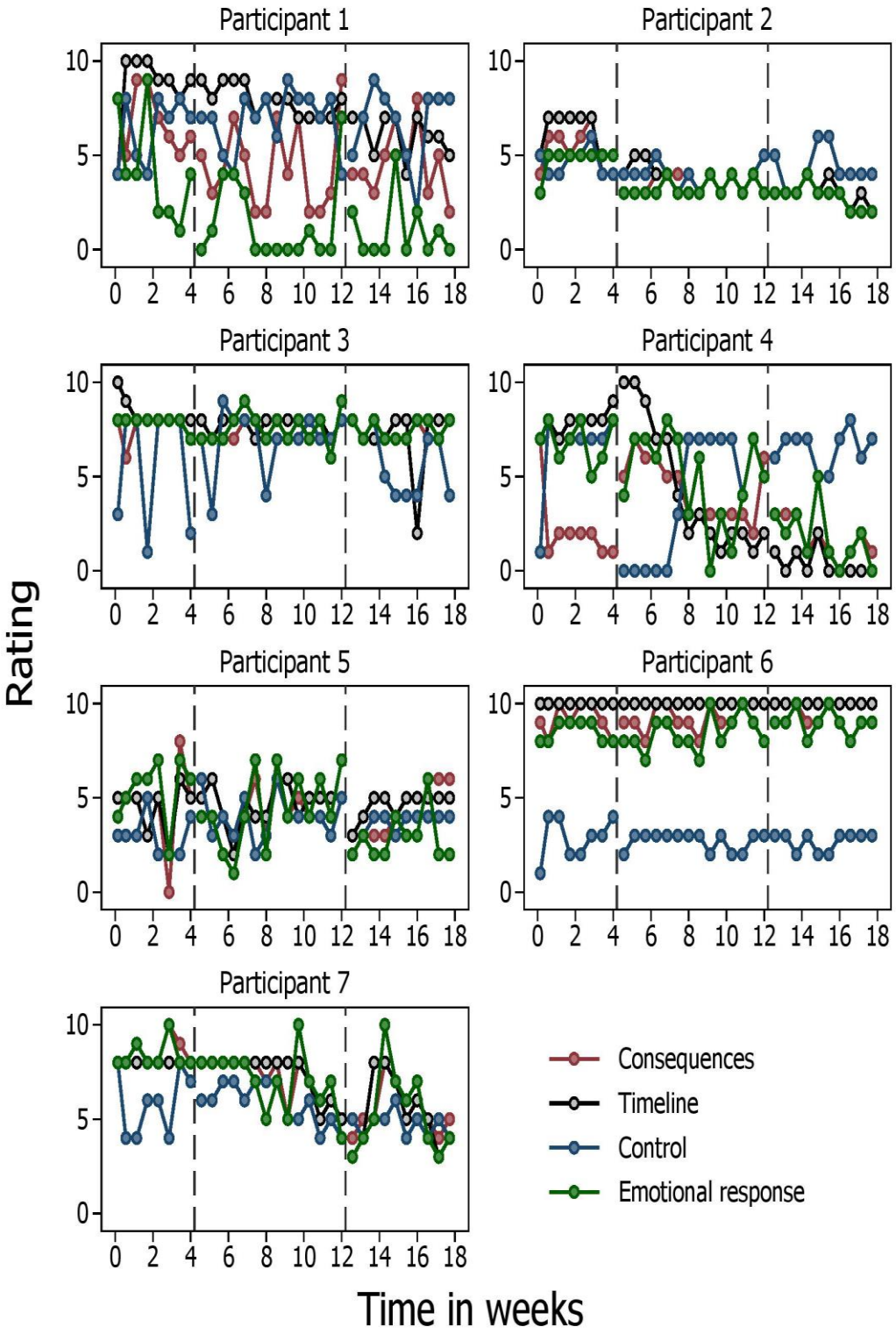


Figure 12: Four-day ratings (0–10) on the Pain Perceptions Questionnaire (BIPQ) at baseline, treatment, and follow-up for participants 1 to 7

Table 4 Key themes specific to individuals and the sample with examples

ID	Themes	Example Quotations
1	1. Getting over the initial, "Oh my god... there's so much to do!"	*"There was quite a lot of information to read and understand, and I felt a bit overwhelmed in the beginning. Only because I was thinking, oh my god, there's so much to do and read and bits of tasks and things I needed to do."*
	2. Goals were like mini projects	*"It was just like having a little mini-project to manage... I'd noticed that on a few days when I didn't get round to doing it [goals], for whatever reason, I could feel the difference. So it was then giving me the motivation to go back and start again… Let's get motivated again and let's get back on track."*
	3. Practise makes natural	*"I probably think its [pain] changed because it was part of my goal-setting activity, and therefore when you do something and repeat it over and over, it just becomes part of your routine… One change would be certain things that I started out as having as goals have now been sort of slotted naturally into my life."*
	4. Bringing self-worth and values to it	*"Also the other thing which came out very early on… probably in the first kind of phone call I had with* [A.H.] *was about self-worth and feeling valued. Because I'm no longer working he helped me to think about it differently and… coming at it from a different angle and somebody saying, actually, just because you're not working doesn't mean to say you can't bring a value to x, y or z."*
	5. Human interaction kept me on track	*"The human interaction side of things… I think that was again a very useful thing. To have somebody to talk to at the start of the programme, and then towards the middle or the end of the programme. So that you knew what you were doing, what was expected and that you were on the track. Otherwise, I think I'm not sure how you would motivate people to stay on track.*
	6. Seeing reductions made me feel less anxious and more in control	*"I think it was a case of, oh actually there might be more to this than I first thought. I think, even if I can get my pain to be a four out of five most days, that has got to be a big upside to it being up to a nine some days and has me in tears. So I think noticing that I was less anxious about my pain levels… I felt that I'd gained a bit of control over it."*
2	1. Pushing yourself does not always mean worse pain	*"I used to be like oh if, it's like it said in the thing* [booklet] *if you overdo it, you think to yourself 'you are going to feel worse tomorrow' but it's not necessarily true really, the whole thing of don't overdo it, like I said and going to bed all the time, just saying, "You know what I am going to try and…" and it has been successful in a lot of ways."*
	2. It's about changing your attitude	*"Like I said it's stuff that I thought about and tried anyway* [strategies] *without being like, oh I know it all, because I don't. It's just that I have realised myself that small changes in your attitude and not just thinking 'oh you know I am going to take my medicine and that is all I can do to deal with MS." Because I think a lot with MS is your attitude… I think changes in mental attitude and just trying to look after your health, your mental health and your physical health, exercise and eating and stuff like that it makes such a difference and a lot of people need help with that I guess."*

	3. It's been hard to keep up with things with work	*"It's been hard to keep up with things because it's been a lot more than I thought it would be, working as well full time, it's been difficult, but yeah I found it quite useful but, to me it's been more of just like, more of an attitude towards things rather than specific exercises itself… I have still yet to do the CD."*
	4. You can't just do it with books can you?	*"I guess it's the type of person, it's the way that your mind works… I did have to discuss it* [booklet] *a little bit, you know working through the whole thing, this kind of programme you can't just do it with books really can you, it does have to involve a bit of talking.*
	5. Being told something different is motivating	[A.H] *would say to me try this week to do some of the things that you maybe would have given up on before. It's just nice to have somebody pushing you in a way. You know, it's like I said, say if I speak to my mum, she is always telling me to go to bed, just go to bed take it easy all the time, and it's just refreshing to speak to somebody and they say, you know what just try and do a few things and see how you feel, it's refreshing to have that kind of motivation."*
3	1. It stopped me falling back into negative cycles	*"I think it's helped me with the planning, it's helped with me, with my feelings towards the planning. It's helped me with my state of mind. It's helped me sort of find a way to approach doing those things without just feeling flattened by it afterwards and going back into one of those awful negative cyclical acts."*
	2. I hadn't put it into words	"*The other thing I thought was really good was, as well as like giving, setting goals and tasks, was trying to identify the ways that you think. Because I knew that I was thinking in a very strange way and I knew I was behaving- I knew what was happening in this kind of negative cycle but I hadn't really identified, or I hadn't got the sort of titles to name those ways of thinking."*
	3. Values-based goals are back on the radar	*"My exercise goals too - I really wanted to achieve that because that is part of my identity and very much linked-up with my values and the way I want to live my life… I think instead of my days just being about work and collapse, it feels like I've got work, and then I try quite hard to then fix on the other things."* *"You know there's a whole chapter on your values and making sure that your goals linked with your values - the ways that you live your life. That was a whole different way of looking at it for me. So, that's what I've tried to do. Bring in more of those things. So going to art galleries and going out into nature, seeing more friends that aren't local to where I live. Those are all part of my values."*
	4. Mindfulness helped with goals	*"It's pretty dull being on an exercise bike. Trying to fill the time up with, like, quite often I think about my work or jobs I've got to do, so I almost start kind of reliving my work. So, I tried to stop doing that and tried to focus on my, you know my legs going round on the pedals, actually doing the sort of living in the moment of being on that exercise bike and listening to the outside sounds and enjoying that."*
	5. Not completely panicking	*"One thing is that doing the exercise does often make the pain worse initially. So I've tried to look at that and think, instead of just completely panicking, like I normally do, I've tried to think, OK* [person's name]*, you know, I often use the words, well it was worth*

		it."
	6. Changing the way you think and act in eight-weeks is challenging	*"It is quite hard and it is quite a challenge to change the way that you think and the way that you act in eight weeks. I don't know why but labelling them and then trying to think in a different way - I found that enormously difficult, but I could do it. You know, that would be such an achievement, and I'm not saying I have, at all, but I'd like to."* *"I tried to also include some ones [*goals] *that approached my sort of thinking. I've been less good at those. But what I've been quite good at is noticing when I'm doing it – although I'm not sure how good I've been at sort of putting them to one side."*
	7. Playing catch up	*"I had a lot of work building up in the middle of it and a* [current job role] *and, as I said to* [A.H.], *it would have been so easy to just stop because I just thought, oh my god, you know, when I get home I've got to do this, and I'm behind and the mad catch up!"*
	8. When pain ramps up it's harder to apply	*"I think that, you know, for me this course is absolutely fine when the pain is at one level. The second it sort of ramps up, that should be really the time that you imply this book, that you apply this book, isn't it? But somehow, when the pain increases, I find it harder and harder to stick to the book."*
4	1. Encouragement with goals spurs you on	*"He* [A.H] *sort of encourages you and says, yeah, that's brilliant, we're on the right track. So, that spurs you on."*
	2. Pacing and prioritising helped with anger	*"I pace myself more… So if I've got more important things to get done, I get those done and not struggle on. So if I do lots and then I make myself tired, and I can't do the important things and then I get angry with myself, because I haven't done them. So, it is making me pace myself more."*
	3. Resting when in pain opens the gate	*"I've realised the difference of just being in [*pain], *and obviously it's really horrible. But if the pain is the predominant thing then I find it helpful that I don't stop and just rest and do nothing because then I do focus on it and it makes me more anxious and that increases my pain - That opens the gate more* [referring to gate control theory].
	3. Putting it into words	*"Because I've always liked that, you know when other people put it in their words and it's sort of what you you've been thinking, or trying to put into words."*
	4. Mindfulness helped me to let things go	*"On the CD, I liked the one on the river, the leaves on the river. I find that, I found that very, um, I've been doing that a lot, because, because I can just sort of let unhelpful things go, you know."*
	5. Getting other's viewpoint	*"If there was something I found difficult, I'd go talk to my husband and he's very good. So it's quite good to have somebody else's viewpoint, isn't it? Somebody that knows you very well."*
	6. Writing about your feelings was challenging	*"I sort of, I found they* [task sheets] *were hard. But it's just basically because it's writing about yourself, isn't it? A lot of it is your feelings and, I suppose, that, you don't really do that after school."*

5	1. Examples were rarely applicable	*"It is such a varied disease or condition, but I know you've got to cover all, so that's why maybe somebody who's less able than somebody else, maybe having more coverage for them."*
	2. Physical limitations with workbook	*"Some of the books were a bit awkward…The workbooks were probably the one thing that I had the most difficulty with. I think my* [carer] *did more on the workbooks than I did… I wanted to fill them in, but I just couldn't fill them in because they just, you know, about being able to get up and walk around."*
	3. Skype® was personal	*"Rather than see a telephone call, a telephone call just not would've been the same, whereas face-to-face, it's much better, you get a chance to meet the person, know what they're like and they get to know you as well. Uh, so I think the Skype idea is definitely one of the best things to do."*
	4. It gave my brain something to do	*"I was looking towards what's next session, you know? The next questionnaire, the next Skype call, I was always preparing for these things. So it's given me an, it's given me something to be more interested in. It's given me something to think about, use the old grey matter, which is starting to diminish quite a bit… So I used to work a lot and now I don't I feel I get quite lazy... This programme has given me something to think about and I'm now using my brain a lot more and I feel better for it."*
	5. Using distraction	*"Now if something does happen and I do get a bit of pain, then I automatically think back to the process that you're doing and try some of the exercises that* [A.H.] *gave me. You know, using my mind, trying to think of other things and things like that. It's certainly helping me… If you get a pain, it's too easy to just think oh, I've got a pain. I just can't keep my mind off it, whereas now I try and distract myself, think about other things."*

6	1. Remoteness from values was shocking	*"Some were a bit shocking when you had to actually write them down. When you actually see them graphically, as plain as day in front of you it's- The quick exercise on values on page seventy-eight* [values bulls-eye]*… Work, education etc. each question I answered for leisure, relationships, personal growth, were right on the circumference. When you have the circle and you're trying to work your way into the centre of the circle, and graphically you see how far away from it you are."*
	2. Fear of disapproval when working towards valued goals	*"I wanted to paint a lot but I don't want to do it because, I know this sounds crazy, but I won't do it because of my wife. Because of what she'd say, she'd tear me to shreds - I know she'd criticise whatever I did… that's the hardest bit, my wife coming and saying, what the hell are you doing that for? You know. That's what I've got to get over."*
	3. I learnt to absorb or accept pain and not fight it	*"Try and live with it and absorb it… you can't fight it and I'm one of these people and I've lived with this all my life, I'm a bit of a bull at a gate and I get cross with myself. I try and fight things. It's the opposite you've got to do. It taught me to back-off and go the opposite way of what I normally do."* *"It teaches you to look into yourself. To accept pain and it's not finished. You know, life… it dominates you so much and you've got to-. You shouldn't fight it in the way I used to fight it. You've got to absorb it more and that's not to let it dominate you all the time."*
	4. No man is an island (social isolation)	*"It's rather like being on an island and you're a fish that's been thrown up onto this island out of the stream and everybody's in the stream and this island is circular and the river's going round and round this island. All your friends, your colleagues, everybody is swimming in the right race. You've been just thrown up onto the island and you can see them, and every now and then, they wave at you or they might hop on and say, "hello", but that's all and then they go back and swim. You know that you'll never join them and swim again. You will never be in that life again."*
	5. Physical health problems can mean two steps back	*"I went into another urine infection on Sunday evening. They're terrible, I thought I'd had it for three years and it puts you into, virtually an epileptic fit and I had to wait until Monday morning before I got antibiotics… You are completely shattered, you know, you could be paralysed and then within five days you're almost- You've got back to where you were* [referring to exercise-based goals]."
7	1. Stopping myself act on thoughts and fears	*"I'm, sort of stopping myself from doing things, you know related to my thoughts, fears and anxieties… and it's has made me change my behaviours a lot."*
	2. Mindfulness exercises helped ground anxiety and set goals	*"I found the leaves on a stream exercise very helpful, I've used that a lot, and I can use that without the CD now in my head, so I found that was very powerful, which is something that I will do when I've got a moment on my own. I will sit and use that to sort of bring me back down to where I should be if I'm starting to get anxious or trying to avoid pain or setting any goals. So I find that really helps me."*
	3. Unhelpful thought records made me	*"The unhelpful thought record that I sort of had to keep around session five, I think having to write it down sort of made it hit home*

think "Crikey, is this me?"	*more what I was trying to achieve, you know, it was a situation as such. But in the end it actually helped me, but at the time I felt, you know I sat back and read it to myself and I thought, 'Crikey, is this me?' you know."*
4. A new romantic relationship and treatment helped	*"I'm feeling far more positive about life really, because I have met somebody new, and I do put part of that positivity down to the programme actually. It all sort of came at the same time, so I think it helped me. When I look back at it now, and you know, start reading the notes I've written, I can see that my life has improved since those few weeks ago, and I seem to be coping more with the pain and am more able to rise above it and lead a more normal life."*
Themes across the sample	
1. Goals tapped motivation	*"One of the ones* [goals] *is the exercise. I really wanted to achieve that because that is part of my identity and very much linked up with my values and the way I want to live my life."* (Participant 3, RRMS)
2. Human contact kept up motivation	*"Speaking to* [A.H.], *he sort of encourages you and says, 'yeah that's brilliant!' we're on the right track. So, that spurs you on."* (Participant 4, SPMS)
	"Talking to someone that is just going to say, "Oh give it a go" it is more of an objective for you I suppose." (Participant 2, RRMS)
3. Create an online version please!	*"If the whole thing was on a website, you could just click onto the website and choose what you wanted to do. Or if you wanted to click onto links that were in the book. If that was all up on a one website it would be really useful."* (Participant 1, RRMS)

7.3.3 Group Themes

Three dominant themes were consistent across participants (see Table 4). First, many found setting values-based goals tapped their motivation. Second, the majority emphasised that personal telephone contact with A.H. during the programme was instrumental in keeping them motivated. Third, most pwMS found the treatment booklets initially overwhelming and slightly overcomplicated, and frequently suggested a web-based version would be less daunting more accessible, particularly for people with greater levels of disability. Whilst pain ratings did not change for many pwMS, it appears most talked about key therapeutic processes and techniques in an insightful way. However, the varied knowledge and skills described by participants suggests they chose to focus on different aspects of the programme.

7.4 Discussion

The current study aimed to evaluate the potential efficacy of an eight-week telephone supported pilot intervention (GIFT) based on CBT and ACT designed to reduce pain severity and pain interference in pwMS using mixed methods. Underlying psychological factors and processes drawn from an empirically supported model of MS pain were also explored as potential mechanisms of change over 16-weeks.

In relation to our first question, three of the seven participants (1, 4 and 7) showed statistically significant 2 to 3 point reductions in pain severity and, to a greater extent, pain interference after controlling for the influence of autocorrelation, which according to guidance in chronic pain reflects a clinically meaningful improvement (Dworkin et al., 2008). These findings were consistent with other pilot studies (Garinger, 2007; Jensen, Ehde, et al., 2011; Sheppard et al., 2010) and one RCT (Ehde, Elzea, et al., 2015) evaluating cognitive and contextual behavioural interventions for MS pain. The more robust improvements in pain interference is, to some extent, consistent with chronic pain research indicating that functioning can improve independently from pain (McCracken & Morley, 2014). The larger effect sizes observed in pain-related interference for two pwMS (4 and 7) at follow-up might also indicate that they gradually became more competent in practising newly acquired skills, or found cognitive skills taught later in the programme were additionally helpful.

Two of the seven participants (2 and 3) did not appear to benefit from the programme. However, there are possible explanations for this. These participants reported milder levels of disability in the sample and worked full-time, explaining that balancing the programme with their busy working lives was challenging. Participant 2 also reported a much higher level of pain relief from medications at initial assessment compared to pwMS in recent MS studies (Ehde, Alschuler, et al., 2015; Harrison, Silber, et al., 2015), suggesting his pain was already well managed with pharmacological treatments.

Two participants (5 and 6) reported worse pain following treatment. Participant 5 had PPMS and was severely disabled, and his poorer outcomes may have stemmed from his declining physical health during the programme. Participant 6 reported periods of depression and demotivation, which also appeared to be related to recurrent health issues and feeling socially isolated. It is therefore possible that his problems were too complex for a low-intensity self-management intervention focusing solely on pain. Overall, the mixed findings in pain outcomes across the group are consistent with practice-based evaluations of interdisciplinary chronic pain management programmes based on CBT, which show that between 1 in 3, and 1 in 7 (depending on the outcome measure), achieve clinically significant gains at post-treatment and follow-up, whilst around 1% to 2% of patients deteriorate during treatment (Morley, 2008).

With respect to our second question, three pwMS (1, 4 and 7) experienced reductions in pain *and* improvements in secondary psychological processes drawn from our MS pain model (Harrison, Silber, et al., 2015), including pain catastrophizing, negative emotional representations of pain, pain beliefs, avoidance of social activities and, to lesser extent, pain acceptance. Pain catastrophizing was the most robust process of change, where two participants showed decreases at follow-up falling below recognised clinical cut-offs (Wideman & Sullivan, 2011). Findings are consistent with a pilot hybrid emotion-focused exposure intervention for chronic pain (Linton & Fruzzetti, 2014), evidence for potential mediators of change in CBT trials for chronic pain (Turner J.A. et al., 2007; Van Koulil et al., 2011; Williams et al., 2013) and MS fatigue (Knoop et al., 2012). Changes in pain acceptance for pwMS who significantly improved on pain outcomes were mixed. Whilst participants 4 and 7 showed significant increases in pain acceptance at follow-up, participant 1 did not, which is somewhat inconsistent with evidence showing pain acceptance is an important predictor of improved functioning in ACT interventions for chronic pain (McCracken & Morley, 2014). However, this

finding might be explained by participant 1's relatively high acceptance scores at baseline, or that different psychological processes change for individuals.

Participants 2 and 3 also reported large reductions in pain catastrophizing and perceived chronicity of pain in absence of any significant improvements in pain outcomes. It is possible the cognitive elements of the programme were more relevant to these higher functioning participants, whilst pwMS with moderate levels of disability seemed to benefit from cognitive *and* behavioural activation components.

Perceived control of pain is likely to tap self-efficacy (Bandura, 1977), which reflects an important predictor of outcomes in traditional CBT for chronic pain (Kores, Murphy, Rosenthal, Elias, & North, 1990; Turk & Okifuji, 2002; Turner J.A. et al., 2007). However, contrary to some pwMS' experience of *"having a greater sense of control"*, perceptions of control measured by the BIPQ did not change for any participant. When considered in relation to the mixed findings for pain acceptance, this may highlight key differences in the way CBT and ACT address the problem of pain (McCracken & Morley, 2014). Traditional CBT encourages participants to set goals, sometimes related to symptom reduction, which may involve scheduling relaxation, rest or physical activity (Turk et al., 1983). In contrast, ACT encourages the person to take an open and willing stance towards pain in order to pursue valued life activities and deemphasises the importance of pain reduction or control (McCracken, 2006). Therefore, whilst these therapeutic approaches complement each other to an extent, it is possible that our attempts to integrate elements inadvertently conveyed conflicting aims of enhancing control *and* acceptance. For example, cognitive strategies within ACT and CBT (e.g. defusion and thought challenging) have divergent aims (Harris, 2009). Thought challenging is primarily interested in modifying the *content* of pain-related thoughts or beliefs and seeking alternatives, whilst defusion focuses more on changing the *context*, or person's relationship to their thinking, without directly attempting to modify or control thought content. From a practical perspective, developing skills in either strategy is likely to require regular practise. Whilst participants were given the option to focus on one or both of these strategies in the programme, learning numerous techniques from both approaches may have diluted opportunities for more targeted learning and practise in either method. Testing a hybrid treatment also makes it difficult to disentangle which methods influence particular psychological processes.

Our final aim was to explore participant's views of the GIFT programme within a post-treatment qualitative telephone interview. Individual themes were not entirely consistent with quantitative findings. Whilst all pwMS found the programme *"beneficial"*, only three reported significant improvements in pain outcomes, and five in psychological processes. Other non-specific treatment factors may have contributed to this, including helping participants make sense of their pain ("*Putting it into words"*). Group themes tended to focus on delivery methods. Most participants described the treatment booklet as initially overwhelming and overcomplicated. However, qualitative themes indicated that most individuals understood key concepts or techniques specifically taught within the programme. It may be that the limited time affected motivation and precluded learning of new skills in those pwMS who were more likely to benefit. The majority of pwMS expressed a preference for a more user-friendly web-based version of the treatment booklet. However, *"Human contact"* with the therapist during the programme was highlighted as an important factor in maintaining motivation. This is consistent with a pilot RCT evaluating an online CBT intervention for MS fatigue with limited telephone support (MSInvigor8) (van Kessel et al., 2008), showing large significant improvements in fatigue severity, anxiety and depression, and quality-adjusted life years compared to standard care (Moss-Morris et al., 2012). Van Kessel et al (van Kessel et al., 2015) recently conducted an RCT comparing MSInvigor8 with or without personalised email support, where pwMS receiving support experienced significantly greater reductions in fatigue severity and impact. Therefore, given the limited resources in most healthcare settings, and disease-related obstacles to access, developing a web-based version of the GIFT programme may improve usability, optimise skills-learning, and reduce pain and related disability in pwMS.

Consistent with our MS pain model (Harrison, McCracken, et al., 2015; Harrison, Silber, et al., 2015) and other chronic pain conditions (McCracken & Yang, 2013), there were no obvious patterns of change related to disease characteristics (i.e. type of MS or pain). Factors affecting individual's negative outcomes appeared to be more associated with social and work factors (participants 2 and 3), and other complex consequences of illness (e.g. pneumonia and depression in the case of participants 5 and 6), rather than nature of pain, level of pain-related disability or MS subtype. Whilst these factors may have contributed to lower levels of participation, it is also possible that pain severity and impact may have been major determinants of both response to treatment and participation.

7.4.1 Treatment Implications

Findings offer some support for a telephone-delivered guided self-management hybrid ACT and CBT intervention based on an empirically-supported conceptualisation of MS pain (Harrison, Silber, et al., 2015). Because participants talked about the complexity of the intervention, it might be that giving pwMS more time to complete each session will help them to practise key skills. Eight weeks may have been too time-pressured, particularly for those pwMS with full- or part-time work commitments. Findings also suggest that pwMS with more complex problems might not benefit from a low-intensity programme. Given that two people got worse, it may be these broader social contextual issues reflect important barriers to participation in this low-intensity intervention. Therefore, adding these factors to MS pain model may better guide future implementation by screening for work, social and other complex health issues prior to treatment to avoid poor outcomes. Specifically, pwMS who work may benefit from having more time to complete the programme, since self-management approaches can be more flexible in this regard. On the other hand, individuals with more complex social problems may benefit from a higher intensity intervention with greater therapist contact.

In any case findings warrant further investigation within a larger RCT. The changes observed in psychological processes indicate that RCTs should test theoretically-guided mediators and moderators of treatment and outcome to better understand how they work, and for whom. Although our cross-sectional data (Harrison, Silber, et al., 2015) indicated variables from both ACT and CBT models explained important variance in pain outcomes, embedding choice within the intervention by combining potentially divergent treatments may have diluted key mechanisms of action specific to each approach. Therefore, it may be helpful to evaluate CBT and ACT independently in the context of MS pain, or provide tailored or optional pathways for one or the other within a web-based programme.

7.4.2 Limitations

This study has several limitations. The incompletely controlled and non-randomised nature single case series studies preclude definitive causal interpretation and are limited in reliability and generality until they are replicated and extended. However, RCTs are at risk of aggregation bias, which assumes the average characteristics of a group apply

to individuals (Johnston & Johnston, 2013). Therefore, whilst not definitive, the current study does explore if, how, why and when the current intervention is effective for particular individuals (Borckardt et al., 2008). Self-report ratings, disease measures and interview responses may be susceptible to measurement, non-specific treatment or therapist effects, and exaggeration or under-reporting. Using group-validated scales may also reduce their reliability, and the neuropathic pain measure (S-LANSS) (Bennett et al., 2005) is yet to be validated in the MS population. Interpretation of findings related to pain subtype should therefore be considered preliminary.

SMA has several limitations (Borckardt & Nash, 2014). First, the autocorrelated adjusted p-values may be too stringent (Nash & Borckardt, 2011) and further research needs to verify it is capable of reliable Type-I and -II error performance with short autocorrelated data. Second, SMA assumes simulations generated are representative of the "population" of data streams from which one's actual data is drawn. However, there is a lack of standardised indices regarding the fidelity of simulations generated, so caution must be exercised when making inferences (Borckardt & Nash, 2014; Nash & Borckardt, 2011). Third, there is a lack of evidence to verify SMA's performance with skewed data or data with extreme outliers. Fourth, simulations of SMA show reliable *AR* estimates with 5 to 30 data points per phase. These ratings are typically recorded at daily intervals, suggesting a standard length of baseline and treatment may range between 5 to 30 days (around 1 to 4 weeks). Therefore, the small phase-*n* sizes and four-day interval between ratings within the 4 week baseline, 8 week treatment and 4 week follow-up phases in the current study may have produced inaccurate *AR* estimates. Potentially inaccurate *AR* estimates might explain why only 40% to 50% of identified effects remained significant when imputing a more conservative *AR* estimate. However, other available statistical methods also have weaknesses. For instance, evidence suggests ITSACORR (Crosbie, 1993) does not match SMA's ability to protect against Type I errors whilst providing sufficient power to detect effects (Borckardt et al., 2008). In addition, other approaches (McKnight, McKean, & Huitema, 2000; Box & Jenkins, 1970) require a much larger number of data points per phase (>30), and some do not appear to have been widely tested or adopted in the case series literature (McKnight, McKean, & Huitema, 2000).

7.4.3 Conclusion

A low-intensity eight-week telephone supported self-management intervention, drawing on techniques from traditional CBT and ACT approaches, may potentially reduce pain severity and pain interference in some pwMS. Whilst the programme was acceptable to all participants, pwMS with milder disability in full time occupations apparently did not have sufficient time to engage in the programme to gain benefit, whilst pwMS with severe physical disability and more complex psychological problems had worse outcomes. Future research may benefit from evaluating the two therapeutic approaches independently, using a web-based format with therapist support that can reach a larger number of pwMS who experience troubling or disabling pain.

Chapter 8 : Discussion

8.1 Chapter Overview

This final chapter first provides a brief summary of the main findings from each of the empirical studies. The novel contributions of the overall research programme are then summarised, followed by a discussion of the theoretical implications for understanding the psychosocial predictors of pain in MS in relation to the previous literature. Potential limitations of studies are then discussed. Finally, possible avenues for future research and clinical practice to improve pwMS' management of pain are outlined.

8.1.1 Summary of main findings

This thesis aimed to develop a conceptual model to guide the development and evaluation of a treatment to support pain management for pwMS. It began by introducing MS and provided a brief overview of evidence for psychological approaches aiming to better manage this complex and heterogeneous condition. Chapter 1 also indicated that psychological approaches for a number of symptoms, including depression, adjustment and fatigue, appeared to be beneficial for pwMS in reducing the severity of symptoms and their negative impact. However, the review highlighted that there had been few attempts to develop an empirically supported theoretical model of MS pain to guide the design of treatments aiming to improve pain management.

The critical review of psychological approaches for primary, non-disease related chronic pain conditions in chapter 2 showed that there were many ways of conceptualising psychological responses to pain. Specifically, there appeared to be several theories of chronic pain, which were potentially useful to explain how psychological factors or processes influence pain and related disability in the context of MS, elucidating possible targets for psychological treatments. The review indicated that whilst the majority of research had evaluated traditional CBT in chronic pain, evidence for more recent theoretical frameworks, including ACT's psychological flexibility model appeared to be comparable. It also concluded that no single theory provided a comprehensive explanation of chronic pain that fully integrated all potentially important psychological variables in the chronic pain cognitive behavioural literature. Therefore, rather than testing a single existing chronic pain model in the context of MS, this thesis

focused on developing a more integrated model and treatment for pwMS using a more inductive approach to inform the design of empirical studies. Ultimately, it was hoped this approach would promote greater choice for pwMS.

As several psychological factors or processes were thought to be involved in MS pain, a working theoretical model was developed to begin to organise key elements of existing theory and research. The systematic review in chapter 3 (Harrison, McCracken, et al., 2015) investigated psychosocial factors in MS pain. These findings led to the development of a preliminary model, which showed that several potentially modifiable psychosocial factors were associated with greater pain and related disability in MS. Specifically, those pwMS who viewed pain as serious or harmful, long-lasting, or felt they had a reduced control over pain, and tried to suppress pain-related thoughts, tended to report greater pain severity and pain interference. In addition, greater reporting of perceived solicitude on the part of others and higher levels of worry, anxiety and depression, were also related to greater pain and related disability. In contrast, pwMS who tended to focus less on trying to reduce or control their pain, pursued meaningful activities in spite of pain, and had more supportive relationships, reported less pain and higher functioning. Avoidance in the context of pain-related fear appeared to be less important in MS pain than has been shown in primary chronic pain. A small number of studies showed that correlates were similar for pwMS with neuropathic and non-neuropathic pain. Consistent with the chronic pain literature reviewed in chapter 2, findings offered support for the idea that several psychological theories might help to explain or predict pain in MS and may be amenable to change in the context of CBT and / or ACT interventions. The weight of evidence was more robust for traditional CBT factors. However, the fact that CBT variables were more carefully and frequently researched compared to other theoretical frameworks did not in itself suggest that the CBT model was necessarily better at explaining pain in MS.

The three remaining empirical studies within this thesis adopted a range of methods to investigate different questions about the psychosocial factors and processes involved in MS pain. First, the qualitative interview study in chapter 4 suggested that pain interacted with other MS symptoms, and pwMS used vivid descriptions to convey their painful experience to others. PwMS also described how they viewed pain as unpredictable, or as a sign of worsening MS, and difficulties with managing frustration and anger as a consequence of pain were particularly common. Consistent with findings

in the systematic review (Harrison, McCracken, et al., 2015), the inductive thematic analysis suggested that pwMS either attempted to manage pain by attempting to control or reduce it, or incorporated pain into their life. Those who struggled to control or reduce painful symptoms appeared to get caught up in vicious cycles of worsening MS symptoms and distress. The qualitative findings also indicated that pwMS may have a tendency to avoid everyday activities when in pain, but avoidance in the context of fear, which has a larger cognitive and affective component, appeared to be less important. This distinction is important because avoidance may reflect pwMS' beliefs that behaviours are potentially helpful or unhelpful, rather than a reaction to fear.

The cross-sectional study presented in chapter 5 demonstrated that a number of cognitive and contextual behavioural factors or processes, drawn from chronic pain models, were significantly associated with pain severity and pain interference in MS. Consistent with findings in the wider chronic pain literature, negative catastrophic beliefs about pain and its consequences and chronicity (Moss-Morris et al., 2007; Sullivan, 2001), avoidance of physical and social activities due to pain (Hasenbring et al., 2014) and low mood were the strongest correlates of worse pain outcomes. Conversely, greater pain acceptance was strongly associated with lower levels of pain severity and pain interference. Overall, psychological variables shared stronger associations with pain interference compared to pain severity. Taken together psychological factors accounted for almost a third of the variance in both pain outcomes after controlling for demographic and disease variables. In addition, contextual and cognitive behavioural variables still accounted for a significant proportion of the variance in pain and related disability even after removing anxiety and depression from the equation. Moderation and subgroup analyses also indicated that the pattern of psychosocial correlates observed were similar for neuropathic and non-neuropathic pain subgroups, but the neuropathic pain was more strongly related to disease factors as well. Most pwMS reported significant pain and associated disability even though over 90% were taking pain medication. Pain was considered the fourth most interfering MS symptom, and was significantly correlated with all other symptom interference ratings.

Finally, chapters 6 and 7 outlined the development and evaluation of telephone supported hybrid CBT and ACT self-management intervention for pwMS with pain based on the updated model. The GIFT intervention was targeted to a broad range of pwMS because the previous empirical studies did not indicate any clear distinction

between pwMS with different types of MS or pain. Whilst other empirical studies in the thesis supported the MS pain model, the intervention study produced mixed results. Findings showed large improvements in pain outcomes for three pwMS, whilst two did not change, and two worsened. The mixed outcomes appeared to be related to the varied levels of participation in the treatment across individuals. Participation appeared to be influenced by extraneous factors, such as occupational commitments for non-responders, and additional health issues and complex social circumstances for those who worsened, rather than type of pain or MS. Whilst three pwMS observed changes in both pain and psychological processes that were consistent with the model, two reported positive changes in targeted psychological processes even in absence of changes in pain outcomes. The most robust change was in pain catastrophizing, but improvements in pain outcomes appeared to be related to changes in different psychological factors or processes across individuals. The qualitative interviews following treatment indicated pwMS had good insight into treatment techniques or methods, although qualitative comments about improvements related to the programme were not always consistent with quantitative outcomes. Specifically, qualitative data indicated that pwMS applied several strategies taught within the intervention, and felt they experienced changes in pain outcomes or relevant factors and processes. However, the quantitative findings did not always indicate this. The day-to-day variability in pain reports may, to some extent, explain this inconsistency. It may also be the case that pwMS felt they were managing pain better even though it was not reflected in their pain outcomes. PwMS also felt overwhelmed with the GIFT manual, and expressed a preference for a shorter web-based version of the intervention. Overall, findings showed that developing a low-intensity hybrid treatment using telephone delivery methods, informed by an empirically supported model of MS pain, may improve pain outcomes for some pwMS.

8.1.2 Contributions to the literature

The studies outlined in the current thesis make a distinct contribution to the literature.

The systematic review had an important role in identifying all existing research examining relationships between psychosocial factors and pain severity and pain interference in MS. Whilst one systematic review had focused on pain in several physical conditions and identified two MS studies (Jensen, Moore, et al., 2011), no previous review had specifically investigated MS pain. Assessing the methodological

quality of the 31 empirical studies provided useful insight into those studies that made the most valid and reliable contributions to understanding the role of psychosocial factors in MS pain. In contrast to previous reviews, the synthesis of evidence brought together variables from several theoretical frameworks in chronic pain and MS research to inform the development of a preliminary cognitive and contextual behavioural model of MS pain. Whilst Kerns had proposed a broader biopsychosocial conceptualisation of MS pain (Kerns, 2000; Kerns et al., 2002), no previous research had provided an empirically supported model that described the possible contribution of specific biological, cognitive, emotional, behavioural and environmental factors. The model also distinguished between those factors or processes that may be more or less helpful in this context.

The review adds to the existing MS pain literature by putting into context several research studies. Alone many of these studies only examined a couple of psychological variables in isolation, and did not provide a coherent explanation of how these factors or processes interact to maintain worsening pain and related disability. The model was also novel because it incorporated a range of possible biological factors as key components that may interact with other components. In contrast to some chronic pain theories, the MS pain model suggests there may be a dynamic and reciprocal relationship between elements of the model and MS-specific factors, including the presence of other symptoms, relapse and disease progression. As far as we know this is the only MS pain model that has integrated all existing psychological targets that may be amenable to change within cognitive behavioural interventions. It is hoped that future research will further investigate the role of key mechanisms within the model, and move towards a more fully integrated account of MS pain, to inform the development of novel clinical interventions in this area.

Previous qualitative studies in MS offered useful insights into how pwMS' describe their pain and its impact (Douglas, Windsor, et al., 2008; Saverino & Solaro, 2010). However the qualitative study in this thesis was the first to ask pwMS about their responses to pain and how they try to manage it. Most of the inductively-derived themes were consistent with psychosocial variables identified in the systematic review, which provided support for the idea that the model represented a helpful way to conceptualise MS pain. The study also added further coherence to the model, where our previous understanding was limited only to quantitative sources. The qualitative study also

enriched our understanding of MS pain by providing new insights that had not been identified in the previous MS literature, including management behaviours related to pain acceptance and reduction, frustration and anger, and beliefs related to pain's unpredictability, causes, and progression. This study highlighted the potential importance of additional psychological factors or processes that might predict and explain pain outcomes. It was the first qualitative study to purposefully sample pwMS with a range of demographic and disease characteristics, which was important because it showed that themes were similar across individuals. It was also the first to explore themes related to psychological responses across pwMS with neuropathic and non-neuropathic pain, but that further quantitative investigation was needed. Exploring potential differences in pain of neuropathic and non-neuropathic origin was important because most psychological theories in chronic pain appeared to be based on non-neuropathic (musculoskeletal) pain, and did not distinguish between the two groups.

Several psychological variables identified in both reviews, and qualitative study appeared to be important in MS pain, but had received less research attention to date. The large cross-sectional study directly tested key elements of the model by investigating whether a range of contextual and cognitive behavioural variables correlated with pain severity and pain interference in MS. No previous MS studies had examined cognitive fusion, pain beliefs and different types of behavioural avoidance in MS. In contrast to many studies in the systematic review, the cross-sectional study examined psychological factors or processes conjointly to provide a more coherent picture of how they fit together in MS pain, and how they interact with relevant disease variables. The cross-sectional study also identified those variables that might be more or less important in explaining pain severity and related functioning. In line with the review chapters, findings showed that a range of potentially modifiable psychosocial factors or processes from chronic plain theories played an important role in the context of MS pain. Therefore, this study further reinforced the idea that the integrated conceptual model outlined in the systematic review represented a helpful way to understand MS pain. The cross-sectional survey was also the first to show that the pattern of psychosocial correlates of pain were similar across pain subtypes. The cross-sectional study therefore offered further support for the idea that a more widely targeted treatment may be helpful for pwMS with different types of pain.

A final important contribution of the current thesis was that it showed improvements in pain severity and interference outcomes were often related to changes in a potentially modifiable psychological factors or processes drawn from the model in the context of a hybrid cognitive behavioural intervention. These findings were mostly consistent with other CBT and ACT intervention trials in chronic pain, which show that pain catastrophizing is an important mediator of treatment and outcome (Trompetter, Bohlmeijer, Fox & Schreurs, 2015; Turner, Holtzman & Mancl 2007). Whilst the literature showed that three preliminary studies (Garinger, 2007; Jensen et al., 2009; Jensen, Ehde, et al., 2011) and one RCT (Ehde, Elzea, et al., 2015) investigating the CBT and ACT interventions for MS pain were potentially efficacious, most were therapist-intensive. In contrast, this was the first study to evaluate a hybrid CBT and ACT self-management intervention for MS pain informed by an empirically supported model. It was also the first hybrid intervention study to explore whether the role of pain-related acceptance, pain beliefs and avoidance behaviours were potentially important processes of change related to improvements in pain outcomes. A recent study tested an eight session telephone-delivered CBT intervention to improve pain interference in MS (Ehde, Elzea, et al., 2015). However, the GIFT study was unique because it was the first to explore the potential efficacy of a low-intensity self-management intervention with only three sessions of telephone support to address potential economic barriers to long-term implementation.

8.1.3 Theoretical implications

The updated MS pain model in chapter 6 resembled a more traditional five-part CBT framework (Beck, 1991), which showed that biological aspects of pain, and potentially helpful and unhelpful modifiable cognitive, emotional, behavioural and social or environmental factors were important determinants of pain severity and reducing functioning in MS. In contrast to some chronic pain theories (Hasenbring & Verbunt, 2010; Vlaeyen & Linton, 2000), relationships between key elements in the model were hypothesised to interact in a reciprocal way to maintain pain and related disability, rather than following any specific causal pathway. The model was less explicit about how an individual's response to MS pain depends on their learning history, personality, critical events or life circumstances, and pre-existing vulnerabilities. However, consistent with Kerns' earlier conceptualisation (Kerns, 2000; Kerns et al., 2002), and most psychological theories described in this thesis, the model incorporates basic

learning principles and assumes predisposing factors are important. The model also acknowledged the wider interactive context of pain in relation to other inherently painful (e.g. optic neuritis and spasticity) or non-painful MS symptoms (e.g. fatigue and immobility), and suggested that pain can potentially be exacerbated by use and overuse of both generic MS treatments (e.g. steroids) and medications prescribed for pain-relief. The empirical studies in this thesis mostly supported the MS pain model. Consistent with the chronic pain literature, the model offered no clear indication that elements drawn from any single dominant chronic pain theory were necessarily more important in explaining MS pain. Therefore, whilst the model offered further support for the idea that either traditional CBT or ACT treatments may be effective for pwMS, it was less clear which approach was likely to be more helpful.

The hybrid GIFT intervention produced somewhat inconsistent findings, which may have important theoretical and treatment implications (for treatment implications see section 8.1.5). Specifically, pain acceptance and, to a lesser extent, perceived control, were robust correlates of pain outcomes in the systematic review and cross-sectional study. In addition, themes around pain management behaviour in the qualitative interviews reinforced the idea that reduced pain acceptance and perceived control were important processes (Harrison et al., 2014). However, whilst the GIFT intervention indicated the most robust change was pain catastrophizing, consistent with the CBT for chronic pain intervention literature (Burns et al., 2012; Smeets et al., 2006; Spinhoven et al., 2004; Turner J.A. et al., 2007), the programme did not appear to alter pain acceptance or perceived control. This finding was inconsistent with processes of change observed in studies evaluating CBT or ACT interventions in the wider chronic pain literature (Åkerblom et al., 2015; Kores et al., 1990; McCracken & Gutiérrez-Martínez, 2011; Turner J.A. et al., 2007). Therefore, this might suggest that our intervention was not as effective as it could have been, or perhaps was deficient in some way. There may be several explanations for this. First, the intervention was facilitated by the author of the thesis, who is neither a qualified or experienced CBT or ACT therapist, nor a qualified clinical or health psychologist, which is likely to have impacted on treatment competence. Second, there were other important factors that appeared to impact negatively on participation, including comorbidities, work commitments and complex social problems. To expand on just one of these factors, recent studies indicate that MS pain and related functioning tends to be associated with several other comorbidities unrelated to the MS disease process (Fiest et al., 2015; Newland, Lorenz, Budhathoki,

& Jensen, 2015). Whilst the MS pain model considers the wider MS context, it did not adequately capture comorbidity. Given the overlap between symptoms and comorbidities found in MS, it is perhaps unsurprising that other researchers have developed and evaluated telephone-delivered CBT interventions to address pain in combination with several other symptoms, showing some improvement in pain, fatigue and depression outcomes (Ehde, Elzea, et al., 2015).

Third, combining techniques from both CBT and ACT treatments may have been potentially overwhelming or confusing for pwMS. Fourth, eight weeks may have been too short to observe change and three support sessions too few, where pwMS may have benefited from having more time to complete the eight week programme at their own pace. This was consistent with the qualitative findings showing that participants felt the GIFT programme included too much information and expressed a preference for a more concise web-based format. A related explanation for the mixed findings might be that pain acceptance, or perceived control, may be less amenable to change in the context of MS. However, a more likely explanation could be that whilst CBT and ACT approaches share some overlap, the combination of divergent treatment techniques in the GIFT programme may have conveyed potentially conflicting messages about controlling and accepting pain. In addition, the MS pain model attempted to organise a variety of factors and processes from both approaches within a traditional CBT maintenance model, but it is important to note there are differences between *factor* and *process* theories. Key constructs and techniques within CBT and ACT stem from different scientific assumptions (Dougher & Hayes, 2000), which are debated in the wider clinical psychology literature (Hayes, 2008; Hayes & Brownstein, 1986; Vilardaga et al., 2007). Therefore, it might be that our attempts to arbitrarily integrate and target variables from both approaches may have partly contributed to the mixed outcomes observed.

Another interesting finding in the cases series intervention was that a few individuals experienced reductions in cognitive and behavioural factors even in absence of any clinically or statistically significant change in pain outcomes. These findings are somewhat inconsistent with the MS pain model and chronic pain theories, which suggest that shifting or changing specific cognitive and behavioural factors or processes (e.g. pain catastrophizing or acceptance) should correspond with reductions in pain severity or pain interference. It might be that inconsistencies observed between the

qualitative and quantitative findings in the case series reflect non-specific effects. Alternatively, the intervention may have modified other possible pathways to improve wellbeing in MS, which might occur irrespective of improvements in pain, such as reducing emotional distress. It might be that skills or techniques taught within the GIFT programme may have been applied in a more general way by these participants. Another explanation might be that potentially relevant psychological factors or processes described by pwMS in the qualitative interviews had actually improved but were not captured in quantitative measurements used. The intervention included present moment awareness and motivational elements (i.e. values and committed action), which may have corresponded with changes in these processes and promoted more general improvements in emotional wellbeing. For instance, these participants might have committed to valued actions but were not necessarily more accepting of their pain, nor did they report any perceptible change in pain severity or pain interference.

A related gap in the MS pain model is that it focused exclusively on pain-specific outcomes. Pain interference attempts to capture pwMS pain-related functioning across several life domains in order to disentangle its impact relative to other MS symptoms. However, the qualitative data suggested pain is usually caught-up in several other troublesome or disabling symptoms. Therefore, examining the relationship between pain and broader emotional, physical and social-role functioning, or healthcare utilisation, outcomes might tell us something more about its wider impact and whether these change in the context of treatment. One aim of the GIFT intervention was to improve pwMS' engagement in everyday, or other meaningful, life activities by reducing pain interference. However, in reality this is very difficult to evaluate because self-reporting of pain interference cannot provide any certainty that pwMS were actually engaging in more activity. One way to overcome this problem in future trials might be to use other technologies to measure activity, such as pedometers or smartphone apps. These more objective measures could then be triangulated with self-report instruments to provide a more comprehensive picture of potential changes in activity as result of the intervention. However, a large component of goal setting in the GIFT programme focused on values-based goals (e.g. participant 5 acted on his value to be "more sociable" by inviting two old school friends to his home for dinner and drinks). Therefore, more objective measures of physical activity may not always capture goals related to more subtle social activities, and other values-based actions (e.g. being more loving or caring towards a partner by talking about feelings more openly). An

alternative way to address this issue would be to obtain the views of the individual's family, carer, or friends who could also report on pwMS progress with goals. However, this would pose an important ethical issue related to patient confidentiality, and may be particularly problematic if the individual experiences complex social dynamics in the home or work context (e.g. an overly solicitous, or unsupportive, partner or employer).

The model also explained less about the social and biomedical aspects of MS pain and how we might intervene in this regard. It still remains less clear if, and how, social factors contribute to worsening or improved pain and related disability in MS. Whilst relatively small correlations between perceived solicitude, social support and pain outcomes were incorporated into the model after the review, a key theme in the qualitative study appeared to centre on concerns surrounding potential stigma related to pain (i.e. "concealing and revealing"). It is possible this theme reflects pwMS' perceived or actual experiences of stigma, or may be a consequence of self-stigmatising responses. Both appear to be a common experience for people with chronic pain (Cohen, Quintner, Buchanan, Nielsen, & Guy, 2011; Holloway, Sofaer-Bennett, & Walker, 2007; Jackson, 2005; Lennon, Link, Marbach, & Dohrenwend, 1989; Marbach, Lennon, Link, & Dohrenwend, 1990; Slade, Molloy, & Keating, 2009; Werner, Isaksen, & Malterud, 2004). However, few psychological treatments have attempted to directly address these problems and it less clear whether chronic pain and MS populations differ in this regard. Similarly, the relationship between biomedical factors and elements in the model also remain unclear. For instance, much less is known about disease progression and pain, or the short and long-term psychological consequences of taking several pain medications, including potentially painful injectable DMTs.

A final weakness relates to the lack of biology in the MS pain model. The model draws on the traditional Beckian cognitive therapy model (Beck, 1991), and therefore recognises the important role of biology. Empirical studies in this thesis aimed to explore the interaction between aspects of all three elements in the broader "biopsychosocial" framework in some way. Specifically, the model attempted to build on Kerns' earlier biopsychosocial conceptualisation (Kerns, 2000; Kerns et al., 2002), by exploring the role of disease variables, such as relapse and disease status, and level of neurological disability, in conjunction with psychological factors or processes and pain outcomes. Since neuropathic pain was found to be more prevalent in MS compared to other chronic pain populations (Bouhassira, Lantéri-Minet, Attal, Laurent, &

Touboul, 2008; Harrison, Silber, et al., 2015; O'Connor et al., 2008; Torrance, Smith, Bennett, & Lee, 2006), the model also set out to examine potential differences between pwMS with neuropathic and non-neuropathic pain. However, as with all chronic pain theories, there remains a paucity of evidence to explain the role of biological factors in the MS pain model.

The earlier biopsychosocial gate control and neuromatrix theories (Melzack & Casey, 1968; Melzack & Wall, 1996; Melzack & Wall, 1967) attempted to link the role of ascending and descending neuronal connections, supraspinal and cortical mechanisms, as well as biochemical processes. Although the MS pain model has investigated broader disease characteristics related to biology, the current thesis did not investigate neurophysiological mechanisms. An interesting question is whether psychological interventions can actually influence pain physiology directly leading to decreased severity of pain, or whether decreases in pain perception are more directly related to psychological processes. In the context of chronic pain, researchers have started to examine the links between specific cognitive behavioural factors or processes and neurophysiological variables (Campbell & Edwards, 2009; Edwards et al., 2009). In contrast, only one MS study has speculated that lesion sites are associated with neuropathic pain (Österberg, Boivie, & Thuomas, 2005), whilst another has shown that GABA receptor system dysfunction is related to greater extremity pain (Herman, D'Luzansky, & Ippolito, 1992). However, no studies to date have examined the relationship between neurophysiological variables and psychological factors or processes in MS pain. Therefore, investigating relationships between pain physiology and psychological processes may be an interesting avenue for future research.

A related issue is that neurocognitive factors were not examined in the MS pain model. Whilst one review has proposed a neuropsychological model of chronic pain (Jensen, 2010), only a few MS studies indicate that neurocognitive impairments are associated with pain, and findings have generally been mixed (Brochet et al., 2009; Demakis & Buchanan, 2010; Miller, Basso, Candilis, Combs, & Woods, 2014; Newland et al., 2012; Newland et al., 2005; Shahrbanian et al., 2015; Stenager et al., 1991). For example, one study found no impairments in working memory (Stenager et al., 1991), whilst another suggested prospective memory impairments (i.e. remembering to remember) were associated with greater pain severity after controlling for disease factors (Miller et al., 2014). It might be that correlations between the presence and

severity of pain (particularly of neuropathic origin) and global neurocognitive impairments may simply reflect the wider impact of the disease process. Alternatively, Miller et al's finding might indicate that memory impairments in MS could either be due to pain's demand on cognitive resources, such as attention, or that pain directly affects brain structures that contribute to memory (Miller et al., 2014).

Another area relates to information processing and negative affective memory bias (AMB). Consistent with the chronic pain literature (Crombez, Van Ryckeghem, Eccleston, & Van Damme, 2013), MS researchers have suggested that AMB potentially reflects a pre-existing cognitive vulnerability to depression, showing that greater AMB is associated with higher levels of pain and depression in MS (Bruce et al., 2007). Overall, in contrast to the conceptual model of MS fatigue (van Kessel & Moss-Morris, 2006), which assumes demyelination and inflammation are predisposing factors, it is still unclear whether neurophysiological, neurocognitive and information processing variables function as either predisposing or perpetuating factors (or both) in pain, and if they are potentially modifiable in cognitive behavioural treatments.

On completion of the case series evaluation it was felt the final model should retain most of the elements outlined in chapter 6 (Figure 8). The variable changes in psychological factors or processes across individuals, paired with no change in pain outcomes for two pwMS, and worsening pain for two others, provided little clarity on which psychological variables were more or less important. However, it may also mean that processes related to changes in pain are different across individuals. The consistent reductions in pain catastrophizing for some participants strengthened support for its position as one of the most potentially important unhelpful factors in the model. This was also true for pain perceptions (related to perceiving more consequences and viewing pain as long lasting), emotional representations and avoidance of social activities, but to a slightly lesser extent. For reasons previously discussed, the lack of change in perceived control and pain acceptance for all pwMS more likely points to deficiencies with the treatment programme itself, rather than either variable being necessarily unimportant. This is supported by evidence showing these variables consistently share significant moderate to strong associations with pain outcomes in the systematic review and cross-sectional study, and have been shown to be modifiable in the context of treatment for primary chronic pain (Trompetter, Bohlmeijer, Fox & Schreurs, 2015; Turner, Holtzman & Mancl 2007; Van Koulil et al., 2011).

Consistent with the cross-sectional study, the case series intervention revealed few differences between neuropathic and non-neuropathic pain, level of disability and MS subtype. Whilst these elements could be removed from the model, it was felt the small sample of the case series, combined with the limited validity of the neuropathic pain measure (S-LANSS) in both the case series and cross-sectional studies, precluded any definitive conclusions about their role. Therefore, whilst the model continues to highlight the potential importance of most variables outlined in chapter 6, it also suggests future studies should further evaluate the role of disease and pain-related variables, and investigate other potentially important factors or processes from CBT (e.g. self-focused attention) and ACT (e.g. committed action, values, present moment awareness), particularly if these approaches are evaluated separately at a later stage. Finally, although the case series highlighted the potentially negative role of comorbidity, work and complex social problems in contributing to reduced participation in treatment and poorer outcomes for some pwMS', there is currently insufficient evidence to support these relationships. Therefore, future research may benefit from examining these potential moderators to further refine the model.

8.1.4 Limitations

8.1.4.1 Systematic review

The studies presented in this thesis have several limitations. The broad inclusion criteria for the systematic review, whilst appropriate for the research aims, resulted in the identification of several heterogeneous studies, precluding a more definitive meta-analysis. Most studies were small, cross-sectional and presented only bivariate findings, which along with a general lack of quantity and quality of evidence, limited robust conclusions about the impact of psychosocial factors on pain outcomes. Whilst the MS pain model assumes relationships between these variables are reciprocal in nature, reflecting relevant targets for cognitive behavioural interventions, it is expected that more high quality longitudinal studies will examine temporal relationships to address causal hypotheses in the future and meta-analyses will then be possible. Finally, whilst the review provided a synthesis of quantitative studies investigating MS pain, existing qualitative studies were excluded (Douglas, Windsor, et al., 2008; Saverino & Solaro, 2010) and a meta-synthesis was not conducted. However, the divergent quality

assessment processes for each method would have meant that the weight of quality ratings would not have been equally considered. In addition, the purpose of the review was to examine MS pain confined to definitions of pain severity and pain interference within quantitative studies, but neither definition had been directly explored in the qualitative literature.

8.1.4.2 Qualitative study

After completing the literature and systematic reviews, the qualitative study's inductive analysis was conducted to inform the use of questionnaires within the cross-sectional study. It is therefore possible that prior knowledge of psychological models of pain may have influenced the researcher's interview questions, expectations and hypotheses, resulting in the salience of certain themes being reported with less emphasis being placed on alternative explanations. On the other hand, the reviews provided a useful starting point to develop open-ended interview questions, which could potentially elicit information related to key elements of the model. The ordering of studies also guided theoretical sampling, which explored potential differences between pain types and other disease characteristics. Furthermore, themes identified in the qualitative study were repeatedly checked against the data, and by the researcher's first supervisor and Dr Angeliki Bogosian, to ensure they were grounded in the data. Whilst this method was consistent, it might have been more helpful to include multiple perspectives from people with differing expertise, including PPI members and other non-psychologist researchers or clinicians. Finally, pain syndromes in MS can be varied and highly unpredictable. Therefore, studying pwMS' experience of pain at different time points might have provided useful insights into pain and related functioning, and psychological responses, particularly as the context of relapses, disease progression, and increasing disability changes over time. Whilst this was beyond the scope of the current thesis, it would make a valuable contribution to the literature in the future.

8.1.4.3 Cross-sectional study

The cross-sectional study was sufficiently powered to examine the contribution of several psychological factors or processes in relation to pain outcomes across pain subtypes (Faul et al., 2007; Tabachnick & Fidell, 1996). However, the importance of non-significant psychological factors or processes within the regression models may

have been underestimated due to common-method variance, and path-analytic methods were not used to determine the unique contribution of separate chronic pain models. However, in most cases the psychological variables selected represented only a small proportion of any one model. Therefore, directly comparing the weight of evidence based on an incomplete set of variables may have potentially resulted in a bias towards candidate models with a greater number of factors or processes investigated. Another limitation was the cross-sectional nature of the study, which limits causal interpretation of the relationships between self-reported psychosocial factors and pain. However, evidence from primary chronic pain treatments (Åkerblom et al., 2015; Kores et al., 1990; Moss-Morris et al., 2007; Turk & Okifuji, 2002; Turner J.A. et al., 2007; Wicksell et al., 2010) offered support for the idea that these psychological factors or processes could be modified in the context of MS.

8.1.4.4 Case-series study

The case-series used mixed methods to explore in detail potential processes or change and overall feasibility of the GIFT programme. However, using inductive thematic analysis (Braun & Clarke, 2006) to identify themes at the individual and group level for seven post-treatment interviews may not be considered robust, where experts in the field suggest saturation typically occurs within the first twelve interviews (Guest et al., 2006). Whilst this limits interpretation of key findings, the themes identified provided richer insights into processes of change, and highlighted inconsistencies between qualitative and quantitative findings at the level of the individual. In the future use of larger samples and established qualitative methods specific to case series intervention designs (Chamberlain, Camic, & Yardley, 2004) may better capture pwMS' experience of cognitive behavioural interventions. Another limitation of the single case series study is that it cannot make any definitive causal interpretations about the efficacy of the GIFT programme, and is limited in reliability and generality. However, due to the exploratory nature of this thesis, the single case series method was helpful to examine the potential efficacy of the intervention for pwMS with a range of demographic and disease characteristics, which can now be refined and extended before being replicated within a larger definitive controlled trial or RCT. Finally, time constraints placed on the thesis resulted in using relatively short data streams over four-day intervals. Whilst statistical procedures used attempted to reduce this problem (Borckardt & Nash, 2014; Nash & Borckardt, 2011), these methods are in the early stages of development.

Therefore, findings should be interpreted with caution, and use of more conventional time series analyses with a greater number of data points would be an optimal method (Robey et al., 1999).

8.1.4.5 Sampling

All studies in the thesis were successful in recruiting pwMS with a range of demographic and disease characteristics from the NHS and several voluntary sector organisations, including the MS UK Register. Although the sample size for the cross-sectional study was large, response rates were relatively low, which may limit generalisability of findings. However, an important strength of this study was that research information was sent directly to all pwMS experiencing pain on the MS UK Register. Recruitment from the register may be more representative of the MS population, particularly when compared to studies that have only recruited pwMS who are currently in contact with health professionals or voluntary organisations. To some extent this would have reduced the potential for self-selection bias highlighted in previous MS research (Dennison, Moss-Morris, et al., 2010; Ferenbach, 2011). Given the large recruitment numbers to the cross-sectional study, and the limited number of temporal designs identified in the systematic review, it may also have been possible to recruit pwMS to a longitudinal design that accounted for high attrition rates. This could have then explored hypotheses for causal relationships between psychological factors and pain outcomes to further test elements of the model. However, limited time and resources meant this was not possible.

In addition, the sample for the qualitative study tended to be older than quantitative samples (24% $\geq$ 61 years of age), and progressive MS subtypes might be viewed as being over-represented. However, representative sampling is not a concept used in qualitative methods. Rather, in accordance with standard qualitative practice (Coyne, 1997; Mays & Pope, 1995), two younger pwMS were purposefully sampled to ensure the views of younger patients were incorporated, and those with progressive forms of MS and men were deliberately oversampled to enhance our understanding of their experience. A similar sampling rationale was applied for the case series intervention study.

8.1.4.6 Self-report of disease characteristics

A further limitation was the self-report instruments used to measure disease variables in all empirical studies. Disease variables, including MS subtype, current relapse, EDSS-S, disease duration and pain type may have been susceptible to either exaggeration or under-reporting by pwMS. Obtaining confirmation from neurologists about pwMS' disease subtype or severity, and relapse status, on entry to these studies would have provided greater accuracy. However, this method would have also been costly and time consuming, increasing participant burden. In addition, there is now reasonable evidence to suggest that pwMS' self-reported disease status is comparable to neurologist assessments (Bamer et al., 2007; Bowen et al., 2001; Gulick, Cook, & Troiano, 1993; Ratzker et al., 1997). One exception was the S-LANSS (Bennett et al., 2005), a self-report measure assessing neuropathic pain used in all studies, which has yet to be validated in the MS population. Therefore, subgroup analyses in all studies should be considered preliminary. However, whilst an MS-validated neuropathic measure has been developed (Rog et al., 2007), it did not provide a cut-off score to define pain subgroups. It was also the case that the proportion of pwMS with neuropathic pain reported in the cross-sectional study fell within the range of other existing MS prevalence studies using different clinical evaluations (O'Connor et al., 2008). Further validation of the S-LANSS in the wider MS population would therefore improve the accuracy of self-reported neuropathic pain within clinical assessment and future MS research.

8.1.4.7 Self-report psychometric instruments

A final limitation relates to the self-report questionnaires used to assess psychological constructs in the cross-sectional study and case series evaluation. Most scales used in these studies have been validated in the MS population, whilst others have not, including the PCS (Sullivan et al., 1995), CPAQ-8 (McCracken, Vowles, & Eccleston, 2004), and AEQ (Hasenbring et al., 2009). It is therefore less clear whether these assessments are measuring the construct they claim to be measuring in the MS pain population. However, these scales showed acceptable reliabilities in the cross-sectional study, and produced correlations with pain outcomes that were consistent with studies in primary chronic pain. A related issue is that all measures used in the case series have only been validated in group-based studies, and have yet to be validated for their use in

single case designs. The frequent completion of these self-report assessments over the trial period may also have resulted in practice effects and self-presentation bias. A final issue was the AEQ total score used in the cross-sectional study. This score was calculated by taking a combined average for *mild* and *severe* pain for both the avoidance of physical and social activity subscales. A.H.'s subsequent email correspondence with the author of the AEQ (Monika Hasenbring) suggested these subscales should ideally remain separate to be consistent with the assumptions of the AE model. However, when checking the cross-sectional data initially, correlations between avoidance behaviours, for mild and severe pain subscales, and pain outcomes were very similar to the combined mild and severe average scores. Overall, further validation of these psychometric instruments in future MS empirical studies would provide greater confidence that they are actually measuring those constructs they intend to measure.

8.1.5 Future directions and treatment implications

In addition to the methodological issues in the previous section, which future research should try to address, the current thesis identified important avenues for future research. These are outlined in the following section.

Despite the potential differences between CBT and ACT treatments, the MS pain model was useful in showing both are likely to be helpful for pwMS. However, the effects in the case series relating to pain acceptance and perceived control were mixed. Therefore, future intervention studies may benefit from evaluating treatments separately. Specifically, other empirical studies in the thesis offered strong support for the idea that pain acceptance is an important process in MS pain. It is also evident that pain acceptance is amenable to change that is associated with improvements in pain-related functioning in the context of both ACT (McCracken & Gutiérrez-Martínez, 2011; McCracken et al., 2005; Vowles, McCracken, & Eccleston, 2007) and CBT interventions for chronic pain (Åkerblom et al., 2015).

Therefore, on the one hand it might be useful to develop an intervention for pwMS that has a larger acceptance component, such as a purer form of ACT. This would more accurately determine if pain acceptance, along with cognitive fusion, can be altered in the context of MS. In addition, the emphasis on values, committed action, and present

moment awareness within the GIFT intervention and pwMS' qualitative data, suggests these processes from the psychological flexibility model may also be important mediators of change within an ACT intervention. However, none of these processes have been tested using quantitative methods in MS pain. Therefore, investigating these additional constructs in preclinical observational and intervention studies evaluating ACT (or CBT) interventions would establish if they are pervasive in MS, and whether they are amenable to change.

On the other hand, the processes of change observed in the case series were generally more weighted towards traditional CBT factors. Therefore, it would also be useful to develop and test a more traditional CBT intervention for MS pain, which focuses more on challenging catastrophic and other pain-specific beliefs and actively promotes self-efficacy. Pain catastrophizing and other pain beliefs, avoidance behaviours, and to a lesser extent self-efficacy, were important correlates and potential mechanisms of change in both pain outcomes in MS. Therefore, focusing on these factors would be particularly helpful if the role of modifying, or reducing, unhelpful responses as mechanisms for reducing pain and related dysfunction is replicated in the context of either a hybrid or more traditional CBT interventions. One additional cognitive factor in the model that has yet to be tested in MS is self-focused somatic attention or symptom focusing, which has been shown to reduce in relation to functional outcomes after a CBT intervention for MS fatigue (Knoop et al., 2012). This cognitive response may also be helpful in explaining MS pain and reflect a potentially important target in the context of CBT for MS pain.

Furthermore, in light of qualitative findings in chapter 4, future observational and intervention research may also benefit from investigating the social element of the MS pain model by exploring the potentially unhelpful role of perceived stigma or self-stigma, and effective ways of changing these. In the broader mental health literature there have been recent efforts to reduce stigma or self-stigmatising attitudes in the context of sexual orientation, depression and substance misuse counselling using ACT and CBT approaches (Griffiths, Christensen, Jorm, Evans, & Groves, 2004; Hayes, Bissett, et al., 2004; Masuda et al., 2007; Yadavaia & Hayes, 2012). These interventions show promise. Therefore, it may also be useful to add a stigma component within either a CBT or ACT treatment for MS pain in the future. Alternatively, it might be helpful to develop brief interventions to shift potentially unhelpful attitudes or behaviours of

pwMS' family, friends or health care professionals. The ACT literature has recently introduced a new intervention method called Focused ACT (FACT), which is specifically designed to shift psychological flexibility processes in the context of short health care consultations (Strosahl, Robinson, & Gustavsson, 2012). Interventions like FACT may have useful applications in this area.

Irrespective of the treatment approach investigated, it seems likely that a broader web format with minimal telephone and / or email support, where pwMS have the choice of participating in one therapy or the other, or a combination, may be an optimal approach. It might be that this choice can be determined solely on a patient preference basis. However, since pwMS may have little knowledge of CBT and ACT, treatment allocation might be more reliably informed by a carefully designed clinical triage or assessment process. The MS pain model is broad and flexible enough to inform such a process, and may also be useful in developing a more tailored formulation and treatment for pwMS that is customised to their pain and current circumstances. Given that some pwMS got worse in the case series, one important question in both the chronic pain (Williams et al., 2013) and MS literature (Thomas et al., 2006) is who is likely to benefit from psychological interventions. The case series also raises the question of when would low- or high-intensity interventions be more appropriate, and should psychological treatments address multiple symptoms or comorbidities, rather than pain alone. These areas are likely to be useful focus of future research. Consistent with CBT trials for MS adjustment (Moss-Morris et al., 2013), disease status and neurological disability did not appear to be associated with improvement in the GIFT intervention. In addition type of pain did not appear to be particularly important. However, findings showed that it may be useful to screen pwMS for other potentially important contextual factors, such as occupational status, comorbidities, and complex social issues, and perhaps neurocognitive problems in line with neuropsychological correlates of MS pain. PwMS with more complex issues may require higher intensity intervention, and those with neurocognitive impairment a simpler approach, or more time, to complete sessions.

In addition, the variable changes observed in psychological processes for both responders and non-responders in the GIFT study suggests that screening for unhelpful beliefs and behaviours at the start of treatment could not only promote choice, but also help the clinician to weight more relevant components of the intervention to the individual's needs. In line with recent findings investigating how people with chronic

pain understand their neuropathic pain (Martin et al., 2014), it may also be important to assess an individual‘s readiness to engage in an intervention and gauge their perception of its relevance to them. In terms of overall acceptability of the intervention, most pwMS felt the programme was informative and found the therapist contact important for motivation. They also appeared have a good knowledge of the exercises or skills taught, and found most of them helpful. In addition, no pwMS reported feeling threatened or stigmatised by the treatment rationale and content, and most said they would recommend it to others. Given that pwMS found the intervention and level of support acceptable, future investigations would also benefit from exploring the clinical- and cost-effectiveness of the either an ACT or CBT, or perhaps a hybrid, intervention in the context of a larger RCT.

Several other issues related to implementation were highlighted after the case series. First, most pwMS found the breadth and depth of the programme content too burdensome, which was particularly true for those who were working full time, had other comorbidities or experienced complex social problems. Second, the patient involvement in the development of the intervention may have been insufficient. Therefore, in the future it might be helpful to obtain feedback from a wider pool of PPI members from different sources with a range of demographic and disease characteristics. Despite these issues, it was felt that one advantage of the guided self-help format was that it could easily be modified for future roll out, by either reducing or simplifying the content for those pwMS who might experience difficulty in successfully completing the programme in its current form. Given the complexity of some of the content in the GIFT manual, another important consideration is whether it could actually be delivered reliably by staff with minimal training. In the future it might be helpful to develop a brief staff training programme, and competency assessment, which alongside the manual and regular supervision from a clinical or health psychologist, may translate to improvements in the therapist’s fidelity to the model and adherence to the manual. A future trial could also compare delivery by staff with minimal training versus those with high level of expertise to compare the relative clinical and cost-effectiveness of these approaches.

There is generally lack of understanding of how psychosocial processes may directly interact with biological elements of the MS pain model. In order to further develop a broader biopsychosocial understanding of MS pain, future research may benefit from

focussing on three potentially important areas that were not examined in the current thesis. First, it may be useful to investigate how psychosocial processes may directly impact on pain physiology (i.e. psychoneuroendocrinology), and whether treatments can actually alter neural pathways. Investigating potential neurophysiological mediators of change in combination with psychological factors or processes from the model in the context of treatment may be a useful approach. For example, MRI studies investigating the effects of cognitive behavioural interventions for chronic fatigue (De Lange et al., 2008), or neurobiological features of mindfulness meditation more broadly (Chiesa & Serretti, 2010), have been helpful to explain if and how treatments work. Similar methods may apply to MS pain, which might incorporate measuring changes in disease progression using MRI scans, physical deterioration and symptom changes, and changes in treatments, in relation to psychological factors or processes in the context of RCTs.

Second, it may be important to consider the implications for theory and treatment in terms of neurocognitive impairments, such as problems with concentration and memory. As one example, prospective memory may limit a person's ability to organise their engagement in meaningful activities, and follow-up on homework tasks or goals set in the context of treatment. Therefore, it might be helpful for researchers and clinicians to assess pwMS' prospective memory, and incorporate this within the formulation process, in order to better tailor the intervention to the individual. This might also involve developing shorter and simpler interventions and giving pwMS more time to complete them. In addition, teaching pwMS compensatory (e.g. simple smartphone reminders), or remedial neuropsychological strategies, in parallel with cognitive behavioural treatments, may help them to remember to complete homework tasks or apply previously learnt skills or techniques in their day-to-day lives.

Third, it may be helpful to further investigate the potential role of information processing biases in the context of MS pain. Similar to research in chronic pain (Crombez et al., 2013; Grumm, Erbe, von Collani, & Nestler, 2008; Pincus & Morley, 2001), this could potentially involve developing cognitive bias modification interventions that help pwMS attend to pain-related stimuli differently, and enhance the effectiveness of cognitive behavioural treatments. This area of research may also link up well with interventions in the chronic pain literature that aim to reprocess potentially traumatic pain-related memories (de Roos et al., 2010; Schneider, Hofmann, Rost, & Shapiro, 2008).

Finally, the role of predisposing vulnerability factors in MS pain remains unclear. It might therefore be useful to understand the impact of early experiences and pre-morbid cognitive and behavioural factors or processes on current cognitive and behavioural responses to pain and key outcomes. Ideally prospective longitudinal designs would elucidate the role of these factors. However, the low prevalence of MS would mean that enormous samples would be required to do this. One way of overcoming this problem would be to employ retrospective longitudinal designs to provide some indication of the importance of hypothesised variables perhaps identified through patient records.

8.1.6 Conclusions

The current research programme underlines the importance of understanding MS pain from a broader biopsychosocial perspective. However, many pwMS have access to biomedical treatments, the emotional burden and impact of pain on individuals and their families may be overlooked in preference for more biological explanations. As the empirical chapters in this thesis have demonstrated, MS pain appears to be multifactorial in nature and pwMS may have a range of psychological responses to pain, which may amplify its severity and have an adverse impact on functioning. No single existing chronic pain theory adequately accounts for all relevant aspects of MS pain. However, a cognitive behavioural conceptualisation that attempts to integrate a range of potentially helpful and unhelpful cognitions and behaviours from existing theories appears to show good utility in terms of understanding pain and informing the development of interventions to improve pain outcomes. The two classifications of pain did not appear to have any clear differential psychological responses associated with them, although disease variables explained neuropathic pain more than non-neuropathic pain.

The preliminary intervention informed by the model demonstrated mixed findings, but modifying specific cognitions and behaviours within the intervention appeared to improve pain outcomes in some cases. Although evidence suggested that changes in psychological responses to pain may follow different pathways for different individuals. The current thesis provides a clear foundation with specific treatment targets from which future intervention research for MS pain can build upon. This work also considered how appropriate interventions should be designed and delivered in the

context of MS to overcome potential barriers to implementation. Research efforts should continue to focus on developing a better understanding of the most relevant factors or processes that influence pain, and which are most amenable to change in relation to pain and other important outcomes. Designing and evaluating either separate or integrated treatment methods to shift these elements may lead to more effective psychological interventions for MS pain in the future.

Appendix A. Chapter 4 Qualitative study: Participant Information Sheet

INFORMATION SHEET FOR PARTICIPANTS

REC Reference Number: 13/SC/0165

KING'S College LONDON

University of London

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET
'Tell me about your pain…' Pain in Multiple Sclerosis (PiMS study)

You are being invited to take part in a research study. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with family members or friends if you wish. Please contact me if anything is unclear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

Who is conducting the study?
This study is part of a larger research project that is being conducted by researchers at The Section of Health Psychology, Institute of Psychiatry at King's College in collaboration with the MS Society UK. The study is being conducted as part of the Principal Investigator (Anthony Harrison's) doctoral studies in conjunction with Lead Investigators Professors Rona Moss-Morris and Professor Lance McCracken. Anthony is being supervised by the Lead Investigators with all aspects of the project.

What is the purpose of the study?
Research has shown that people with MS experience different kinds of pain, but there is little research into how this symptom is experienced by people with MS. We are interested in how people with MS understand their pain, how much it affects them, and how they deal with it from the day-to-day. The researchers also want to talk to people with MS pain about their views on improving pain management, service provision and any other related issues that are important to them. At the conclusion of the study, we will provide you with a newsletter summarising the main findings.

Why have I been chosen?
You have been approached about this study because you have Multiple Sclerosis and have reported to us that you experience some form of pain. We have invited those people with a variety of MS pain symptoms to take part in the project. Unfortunately, volunteering by providing us with your completed questionnaires may not necessarily result in you being interviewed. While we do understand you may feel discouraged by this decision, this is because we aim to recruit 20 people with a variety of illness characteristics to determine if they have different views about MS pain.

Do I have to take part?
No. It is up to you to decide whether to take part or not. Whether or not you take part will not affect the standard of care you receive. If you agree to take part you may be asked whether you are happy to be contacted about participation in future studies. However, your participation in this study will not be affected should you request not to be re-contacted.

What will happen to me if I take part?
After reading this information sheet you must take at least 24 hours to consider if you wish to take part. If you do agree to take part by completing and returning the three enclosed questionnaires and contact details form Anthony Harrison will contact you to arrange a convenient time to conduct a telephone interview. You will be asked to provide verbal consent before starting the interview. The interview will last somewhere between 30 minutes to one hour. The interviewer is not in any way connected with the team involved in your treatment. Anthony will ask you some questions about how

you view your pain, how it affects your life, how you deal with your pain, and what sort of support you find helpful. There are no right or wrong answers - the researchers want to find out about your views and experiences. The interview will be recorded so that the researchers can write these up at a later date. After the interview Anthony will then briefly ask about your demographic and MS characteristics and offer to send you a study debriefing statement either to your home address or personal email.

Will You Compensate Me for My Time?
No. While we very much appreciate your help, and you may find the experience useful, you will not benefit financially from the research.

Are there any costs?
The research will take between 30 minutes and one hour of your time but there are no costs to participants associated with the project.

What are the possible disadvantages and risks of taking part?
The risks involved in participating are minimal. It is possible that some people might find it distressing to talk about their experiences of pain and MS in general. If you get upset you can skip questions, take a break or decide not to continue with the interview. If you are very distressed we will offer you some sources of support.

What are the possible benefits of taking part?
There may not be any immediate or direct benefits to you by taking part. However, some people may find it helpful or interesting to talk about their illness and how it affects them. Your participation will help us to develop a better idea of how we can help people who experience MS pain. At the conclusion of the project, we will send you a newsletter describing the major findings and alerting you to any research publications we have generated from the project.

If this study has harmed you in any way…
In the unlikely event that you are unhappy with the way that the research is conducted complaint mechanisms are available to you. In the first instance please contact Professor Rona Moss-Morris rona.moss-morris@kcl.ac.uk. If you are not satisfied with this process, we advise you contact the Patient Advice and Liaison Service (PALS), at **Guy's and St. Thomas' Hospital's PALS** KIC Ground floor, North Wing, St Thomas' Hospital, Westminster Bridge Road London SE1 7EH (tel. 02071888801 or 02071888803 or email pals@gstt.nhs.uk). **Kings College Hospital PALS,** King's College Hospital, Denmark Hill, London SE5 9RS (tel. 020 3299 3601 or email kch-tr.PALS@nhs.net). **Queen Mary's PALS,** Frognal Pl, Sidcup, Kent DA14 6LT (Tel: 020 8308 5449 email: slh-tr.qm-pals@nhs.net) **Bromley Hospitals PALS,** Princess Royal University Site, Farnborough Common, Orpington, Kent BR6 8ND (Tel: 01689 863252 email: slh-tr.br-pals@nhs.net) **Queen Elizabeth PALS,** Stadium Road, Woolwich, London SE18 4QH **(**Tel: 020 8836 4592 email: pals.qeht@nhs.net).

Will my taking part in the study be kept confidential?
Yes. All information about your participation in this study will be kept confidential in accordance with the Data Protection Act 1998. Once the interview is complete, your name on the interview audiotape and the transcript data will be replaced with a participant ID number making it completely anonymised. Your information will be stored on secure computers, locked within offices and in locked file cabinets, and will only be available to members of the research team. This information will only be used for the purposes of the current study. Your study data will be retained for a minimum of 5-years and subsequently disposed of securely. Once the study is written up and published some quotes from your interview may be used as examples of what people have said. If we use any quotes from your interview they will not contain your name or any identifiable information about you as an individual (e.g. your town or workplace). Your responses to our questions will remain completely confidential unless you tell us something to indicate that your own health and safety are currently in danger. Your

anonymised data will be shared with other researchers and may be used for other research purposes. Please note the deadline to request withdrawal of your data from the study will be 1st June 2013.

What will happen if I don't want to carry on with the study?
You are free to withdraw from the study at any time without having to give a reason even if you decide to take part initially.

What will happen to the results of the research study?
The results will be used to help the researchers better understand MS pain with a view to developing future treatments. The study will be presented at scientific conferences and be written up for publication in scientific journals. We will provide you with a summary sheet of the results.

Who is organizing and funding the research?
The study is funded by the Multiple Sclerosis Society. It is being organized and conducted by researchers from The Health Psychology Department, Institute of Psychiatry, King's College London.

Who has reviewed the study?
The study has been reviewed by the Reading NHS (13/SC/0165) and the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee (PNM/12/13-65), King's College London, as well as the research and development team at the UK Multiple Sclerosis Society.

What if I have questions about the project? Contact details for further information
If you would like to discuss your potential involvement in this research further please contact:

Name: Mr Anthony Harrison
Job title: Principal Investigator (Doctoral Student)
Telephone number: 07936 448 926 Email address: anthony.harrison@kcl.ac.uk

Address: Department of Health Psychology, Institute of Psychiatry, Kings College London, 5th Floor

Bermondsey Wing, Guys Campus, London SE1 9RT

ALTERNATIVELY: Fill in the attached contact details form, return it in a stamped addressed envelope and one of the researchers will contact you

Please retain this information sheet.

Appendix B. Chapter 4 Qualitative study: Consent to Enter Study Form

Participant Identification Number:

KING'S College LONDON
University of London

CONSENT FORM

'Tell me about your pain…' Pain in Multiple Sclerosis (PiMS study) (Study ethics Ref: 13/SC/0165)

Name of Researcher: _____

Please initial at the end of each statement to confirm

1. I confirm that I have read and understand the information sheet (dated 12 November 2012, version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily ..…..

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected …….

3. I consent to the processing of my data in accordance with the Data Protection Act (1998) …….

4. I give permission for the interview I take part in to be audiotaped ...…..

5. I understand that when the research is published it may include direct quotations from my interview but that I will not be identified as an individual ……

6. I agree to take part in the above study ……

7. I give permission for my unidentifiable data to used for future research ……

Name of Participant_____ Date____Signature_____

Name of Person taking consent_____ Date____

Signature_____

(If different from principal investigator)

Researcher_____

Date_____Signature_____

When completed, 1 copy for the patient; 1 for researcher's file

Self-report Version of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS) (Bennett et al., 2005)

About your MS and the pain you experience

I believe my pain is due to:

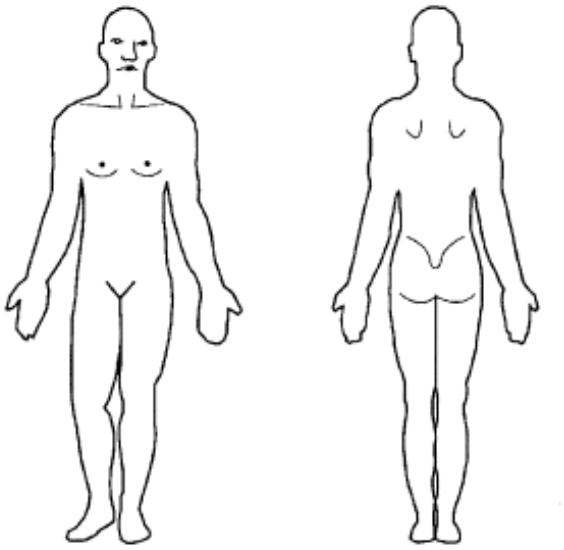
1. The effects of MS treatment.
☐ Yes ☐ No

2. My MS.
☐ Yes ☐ No

3. A medical condition unrelated to MS.
☐ Yes ☐ No

- This questionnaire can tell us about the type of pain that you may be experiencing. This can help in deciding how to treat it.

- Please draw on the diagram below where you feel your pain. If you have more than one area, **only shade in the main area where your worst pain is.**



On the scale below, please indicate how bad your pain (that you have shown on the above diagram) has been in the last week where:
'0' means no pain and '10' means pain as severe as it can be.

NONE 0 1 2 3 4 5 6 7 8 9 10 SEVERE PAIN

- On the other side of the page there are 7 questions about your pain (the one in the diagram).
  Think about how your pain that you showed in the diagram has felt **over the last week.** Please circle the description that best match your pain. These descriptions may, or may not, match your pain no matter how severe it feels.
- Please only tick the responses that describe your pain. **Please turn over**.

1. In the area where you have pain, do you also have 'pins and needles', tingling or prickling sensations?

a) ☐ NO – I don't get these sensations
b) ☐ YES – I get these sensations often

2. Does the painful area change colour (perhaps looks mottled or red) when the pain is particularly bad?

a) ☐ NO – The pain does not affect the colour of my skin
b) ☐ YES – I have noticed that the pain does make my skin look different from normal.

3. Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations of pain when lightly stroking the skin might describe this.

a) ☐ NO – The pain does not make my skin abnormally sensitive to touch.
b) ☐ YES – My skin in that area is particularly sensitive to touch.

4. Does your pain come on suddenly and in bursts for no apparent reason when you are completely still? Words like 'electric shocks', jumping and bursting might describe this.

a) ☐ NO – My pain doesn't really feel like this.
b) ☐ YES – I get these sensations often.

5. In the area where you have you pain, does your skin feel unusually hot like a burning pain?

a) ☐ NO – I don't have burning pain
b) ☐ YES – I get burning pain often

6. Gently <u>rub</u> the painful area with your index finger and then rub a non-painful area (for example, an area of the skin further away or on the opposite side from the painful area). How does this rubbing feel in the painful area?

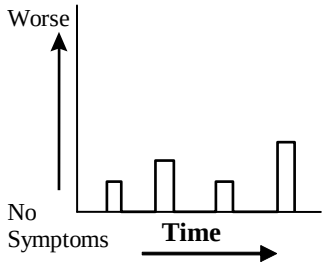
a) ☐ The painful area feels no different from the non-painful area.
b) ☐ I feel discomfort, liker pins and needles, tingling or burning in the painful area that is different from the non-painful area.

7. Gently <u>press</u> on the painful area with your finger tip then gently press in the same way onto a non-painful area (the same non-painful area that you chose in the last question). How does this feel in the painful area?

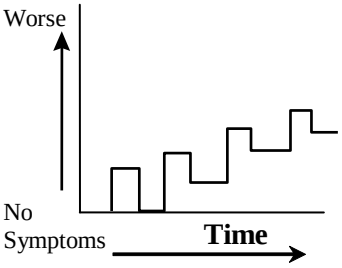
a) ☐ The painful area does not feel different from the non-painful area.
b) ☐ I feel numbness or tenderness in the painful area that is different from the non-painful area.

Self-administered Multiple sclerosis
Disease Course Questionnaire (Bamer et al., 2007)

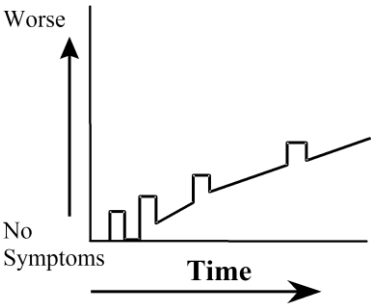
Check *only* one box that best describes your *MS disease activity over time*



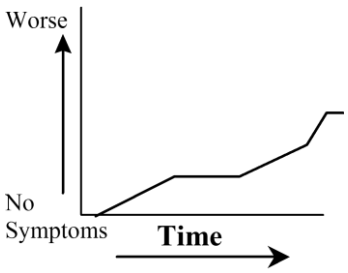
☐ Attacks (exacerbations, relapses) come on over a few hours or days, last from one day to several weeks, but once they are over, you feel the same as you always have.



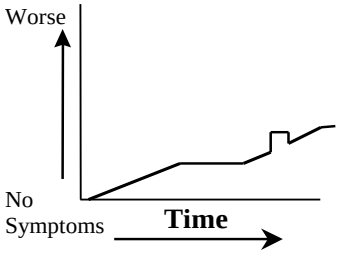
☐ Attacks (exacerbations, relapses) come on over a few hours or days, last from one day to several weeks. After some attacks, your symptoms are worse than before. The symptoms that remain after the attack are stable until a new attack occurs.



☐ At the start of the disease, attacks (exacerbations, relapses) occur. You may feel your symptoms get worse because of these attacks. Then even between the attacks, you feel you are getting worse. In some cases, attacks cease, yet your symptoms continued to worsen.



☐ Symptoms worsen from the beginning. Your symptoms may be stable for a time, gradually worsen, or deteriorate rapidly, but attacks (exacerbations, relapses) have never occurred.



☐ Symptoms gradually worsen from the beginning. Your symptoms may be stable for a time at the beginning, or may deteriorate rapidly. Attacks (exacerbations, relapses) did not occur at the start, but may occur later in the course of the disease.

Self-report EDSS (EDSS-S) (Bowen et al., 2001)

WALKING DISTANCES

We would like to know how well your body functions on an average day, not your worst days and not your best days. Please tick the box that most closely matches your abilities.**

On an average day I can:

☐ Walk more than 500 metres (about 530 yards) without stopping to rest.
(This is approximately 5 football field lengths.)
I would need ☐ no help ☐ a cane ☐ two canes ☐ a walker

☐ Walk 300 metres (about 350 yards) without stopping to rest.
(This is approximately 3 football field lengths.)
I would need ☐ no help ☐ a cane ☐ two canes ☐ a walker

☐ Walk 200 metres (about 200 yards) without stopping to rest.
(This is approximately 2 football field lengths.)
I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

☐ Walk 100 metres (about 100 yards) without stopping to rest.
(This is approximately 1 football field length.)
I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

☐ Walk 20 metres (about 60 feet) without stopping to rest.
I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

☐ Walk 5 metres (about 15 feet) without stopping to rest
I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

☐ Walk a few steps.
I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

☐ Use a wheelchair

If you use a wheelchair please **tick one** of the following 4 statements:

1. ☐ On an average day, I can bear my weight with my legs (stand up and move) and get myself from one chair to another.
2. ☐ On an average day, I can bear my weight (with the strength in my arms) and lift myself from one chair to another.
3. ☐ On an average day, I cannot bear any weight or get myself from one chair to another.
4. ☐ On an average day, I cannot sit up in a chair.

STRENGTH

When answering the following questions, please think about an average day for you (not a particularly good, or bad day) then think of the "best" part of that day. (Maybe the best part of your day is in the morning, or maybe later, after you have moved around a bit.)

On an **average** day, at my **best**, my strength is:

	The same as before I had MS	Almost the same as before I had MS	Can barely raise limb in the air	Can move limb, but not raise it in the air	Cannot move limb at all
Right arm	☐	☐	☐	☐	☐
Left arm	☐	☐	☐	☐	☐
Right leg	☐	☐	☐	☐	☐
Left leg	☐	☐	☐	☐	☐

COORDINATION

On an average day, at my best, my coordination:

	The same as before I had MS	Almost the same as before I had MS	Interferes with some movements, though I can eventually complete them without help	I must get help, use a mechanical device, or brace the limb to complete movements	Prevents me from completing movements even with help.
Right arm	☐	☐	☐	☐	☐
Left arm	☐	☐	☐	☐	☐
Right leg	☐	☐	☐	☐	☐
Left leg	☐	☐	☐	☐	☐

SENSATION

For touch, pain, cold, or heat, please mark the appropriate box in the table below. **Use the worst – the one that has lost the most sensitivity – of the four sensations** (touch, pain, cold, or heat) to answer each question. Please think of an **average** day.
(For example: your left hand has very little sensitivity to pain, mild sensitivity to touch, and normal for heat and cold, then you would mark “can feel very little” on the line for left hand.)

	Same as before I had MS	Mild loss of sensation	Moderate loss of sensation	Can feel very little
Right hand	☐	☐	☐	☐
Right arm	☐	☐	☐	☐
Left hand	☐	☐	☐	☐
Left arm	☐	☐	☐	☐
Right foot	☐	☐	☐	☐

Left foot	☐	☐	☐	☐
Left leg	☐	☐	☐	☐

BLADDER

On an **average** day, I have:

Yes	No	
☐	☐	A normal bladder
☐	☐	Urgency (once I need to go I have a hard time holding it)
☐	☐	Hesitancy (I feel I need to go but nothing happens)
☐	☐	Accidents (incontinence) occasionally but once a week or less
☐	☐	Accidents (incontinence) twice a week or more, but less than daily
☐	☐	Accidents (incontinence) daily
☐	☐	Use self-catheterization
☐	☐	Use continuous catheter (indwelling or condom catheter)

VISION

1. Which line is the smallest that you can read (you can use glasses if needed).

Left eye only	Right eye only	Both eyes together	
☐	☐	☐	937826
☐	☐	☐	428365
☐	☐	☐	374258
☐	☐	☐	428365

☐	☐	☐	Cannot read any of the lines above

2. I see double (two things, where there is really only one)

☐ Never ☐ About once a week ☐ Almost daily
☐ Constantly

3. On an average day, my eye movements are unsteady
☐ Never ☐ Only when looking to the side ☐ All the time

SPEECH

On an average day, my speech is:
☐ The same as before I had MS
☐ Slightly Slurred
☐ Moderately Slurred
☐ Severely Slurred

SWALLOWING

On an average day, my swallowing is:
☐ Normal
☐ Occasional choking
☐ Unable to swallow

THINKING

Although some people may wish to consider thinking and memory separately, we need you to combine them and tick one box below.

On an average day, my thinking and memory is:
☐ Is the same as before I had MS
☐ Is almost the same as before I had MS
☐ Occasionally causes a problem in my daily life
☐ Frequently causes a problem in my daily life
☐ Others have to help me manage my affairs

Appendix D. Chapter 4 Qualitative Study: Post-interview Demographic and Multiple Sclerosis Information Sheet

To be completed over the telephone by the researcher.

Your year of birth: .....

What is your gender:

☐ Female ☐ Male

What is your ethnicity:

☐ White - English / Welsh / Scottish / Northern Irish / British	☐ Mixed / Multiple ethnic group - White and Black Caribbean	☐ Asian / Asian British – Indian	☐ Black / African / Caribbean / Black British – African
☐ White - Irish	☐ Mixed / Multiple ethnic group - White and Black African	☐ Asian / Asian British – Pakistani	☐ Black / African / Caribbean / Black British – Caribbean
☐ White - Gypsy or Irish Traveller	☐ Mixed / Multiple ethnic group - White and Asian	☐ Asian / Asian British – Bangladeshi	☐ Black / African / Caribbean / Black British – Any other Black / African / Caribbean background
☐ White - Any Other White background	☐ Mixed / Multiple ethnic group - Any Other Mixed / multiple ethnic background	☐ Asian / Asian British – Chinese	☐ Other ethnic group – Arab
		☐ Asian / Asian British - Any other Asian background	☐ Other ethnic group – Any other ethnic group
			☐ Not known/not provided

What is your marital status (at present)

☐ Single ☐ Married ☐ Widowed ☐ Separated/Divorced

How many years of education have you completed.....

Which of the following best describes your current job status?

☐ Employed outside the home, full-time
☐ Employed outside the home, part-time
☐ Homemaker
☐ Retired
☐ Unemployed
☐ Other

If unemployed, are you not working due to your MS? Yes ☐ No ☐

MS Characteristics

What type of MS do you have?……
Are you currently experiencing a relapse? ☐ Yes ☐ No
How long have you had MS?……..

What other MS symptoms do you experience currently:
☐ Fatigue
☐ Bowel or bladder dysfunction
☐ Balance disruption
☐ Cognitive impairment
☐ Blurred or double vision
☐ Difficulties with Speech
☐ Difficulties with swallowing
☐ Stiffness and spasms in muscles
☐ Tremor
☐ Sexual dysfunction
☐ Other
……

Do you take medication for your MS pain? ☐ Yes ☐ No
If yes, which?
……

Do you take non-medical drugs for your MS pain? ☐ Yes ☐ No
If yes, which?
……

Other health conditions:

Have you ever experienced (or currently have) any other physical condition other than MS?

☐ Yes ☐ No

If yes, what is the condition/s:……..

Have you ever experienced, or currently experience, any psychiatric condition/s (e.g. depression, anxiety, schizophrenia)?

☐ Yes ☐ No
If yes, what is the condition/s:……..

Appendix E. Chapter 4 Qualitative Study: Coding Manual

Theme label	Subtheme labels and definitions	Examples/locations (by line number)
1. PAIN IN THE WIDER MS CONTEXT	**"Top of the league" for some, but for not all…** Painful symptoms described in relation to other MS symptoms, which might either be highlighted as the worst symptom, or comes secondary to others.	**P4** *"Oh this is, um, well this is top of the league really, is that what you are asking?* [I: Yeah] *It's unrelenting. That's the word I would use* **114***."* **P5** *"If the pain could be sorted out everything* **105** *else* [symptoms] *would be manageable every day but getting to the point of the pain to be sorted out is where hopefully stuff will come in the future."* **P20** *"I would probably say on a scale of one to ten, it's probably about a two because it's there, it's bothering me, you know it's there all the time, that I can't* **270** *do a great deal about it, I just have to manage it, I think my eyes and my legs are my bigger problem, you know they kind of over shadow pain."* **P13** *"The main thing about my illness, is not actually the pain so much as the tiredness, um that's what I find the worse, the absolutely worse think in my illness* **195***"*
	Every move is MS move Pain described as resulting in a disruption, or slowing down, of everyday activities, to the extent that constant planning is required. In some cases this subtheme relates to "common ways to self-manage" because the person may say they need to plan activities carefully	**P10** *"I have got to think twice about if I was walking around to the shop* **312**, *[I: Mm] I might take the car instead [I: Mm] or I might spend more time sitting down, if it is particularly bad."* **P14** *"Okay so if I have to, if I'm doing an installation which takes concentration and will take me three hours and I've allocated that three hours [I: Mm] I expect it, in my working life to actually take me three hours [I: Mm] but if I suddenly get an, um err a pick axe or err pins and needles and I know something is going to start to not work probably or I'm going to get pain, then* **95**

	and schedule rest breaks.	*that interrupts my schedule and I have to allocate time to that and to deal with that."* **P17** *"It sort of affects your day to day life because your, because you are aware of it all the time, you tend to change what you do, you tend to know your limits and know what you are able to do [I: Mm], you know as far as walking distances is concerned, that's a no, no because but then I do get, not only tired but the pain that will come in the lower* **60** *back and the backs of my legs as well."*
	It's not just about pain This includes statements about the problem of pain sitting within a wider context of other problems, such as low mood or other health conditions.	**P4** *"It's all related to the MS that you have got and you are not going to be able to get rid of it, I don't think I am going to be able to get through this, um, you know nothing is going to happen in my life time let's say, so it really gets you down* **199.***"* **P8** *"Well, um, I have the hypermobility, um but I also have, um, I have glaucoma* **135** *as well and it is just a mountain of things that suddenly you know you realise that, oh, you are not young any more, you are not agile, you just carry on with what you perceive to be life, you know, as much as you can."* **P5** *"There are symptoms that I have, apart from the neurological ones and the like um, which are not a pleasant thing to deal with either* **100***."*
	Pain affects you because it's always there Suggestion that some forms of pain being pervasive and very difficult to push out of consciousness.	**P10** *"I do get quite a lot of headaches as well but I think because it is on my feet, I think I am more conscious of it all the time. I mean I live with it and I still work two afternoons a week and I still do most things that I want to do because it does get quite tiring having the pain all the time* **144.***"* **P4** *"Because it's with you* **200** *all*

		the time, every move you make is an MS move, it doesn't, there is no way you are going to get any time off from it, you can't relax." **P13** *"Pain fits in daily… I mean I'm in pain every single day* **65**."
	Pain swirls in with everything else Reports that pain tends to come with a combination of other unpredictable symptoms, including fatigue, sleep disruption, balance, loss of strength and mobility, and in some cases speech or visual difficulties. Specifically, other MS symptoms revolve around pain in the sense that it influences the onset, or is the result of other symptoms, perhaps becoming a common label when identifying or describing symptom experience.	**P21** *"Um so when I say they all revolve around pain, it's that you get different types 80 of pain, maybe the numbness will cause you a pain but it is probably not as high as scale of eight, it's probably more in a scale of one to three, just because of the sensation not feeling so go [I: Yeah] and any sensation that you are not supposed to get in your body just makes you feel pain, I think [I: Mm], maybe it's all in the mind, but I feel like a weird sensation and it causes like interruptions* **85** *to my day [I: Yeah], so I mean, can you call it pain."* **P15** *"Pain is part of the symptom, if that makes sense, that's probably why the symptom is becoming more of an issue rather than, because of the pain within, I think all of my MS symptoms, yeah, every single MS symptom I have ever had was attached to pain* **48**.*"* **P23** *"Everything comes together 212. They all happen at around the same time, and that normally starts to occur the more tired I get, the more stress, the more strain I feel on my muscles, my activity, so the less activity you participate in the less you feel anything."*
2. VIVID AND PARADOXICAL DESCRIPTIONS	**Describing pain can difficult and elusive** This includes statements about finding the experience of pain difficult to put into words or describe, perhaps highlighting that the experience is	**P12** *"Yeah, like a tightness of, you know, yeah, oh man it's so hard to describe these things [I: Yeah], it's like a tightness and again a discomfort. I guess, I guess in my arm and legs I do have that as well, I guess where the comparison* **150** *could be is that there's discomfort an there's discomfort in using a hand or arm or whatever and then there's just the general crampy*

	particularly unusual.	*feelings that I have [I: Mm] which is pain, that's more like a pain, whereas, yeah it is so hard to describe, honestly!"* **P13** *"I don't know how to describe it, I haven't got it, so* **285** *at the moment so it's really hard to actually describe it unless I'm in it or have got it."* **P14** *"I really have no level of how to explain what level of pain I get, um I know compared to other people [I: Mm], and how you describe and other people* **53***?"*
	Elaborate descriptive imagery of pain PwMS use of highly elaborate and sometimes graphic metaphors, analogies or images to describe pain.	**P4** *"In my feet, you know, I could say that um it feels as though somebody is um hammering my feet with a claw hammer, a metal hammer [I: Mm], but how do I know that because that has never happened to me* **75***?"* **P12** *"In my* **360** *hands it's more of a, like I said, like someone is actually stood on my hands, like they, it feels like my bones are crushed or something, it's weird."* **P13** *"The pain I experience is um mainly headaches and nerve pain, shooting pain and pins and needles, um, it* **5** *does feel like somebody is throwing darts at me sometimes."* **P14** *"I have what I call the 'pick axe syndrome' which goes through the top of the head but would generally only last* **15** *thirty seconds, maximum one minute and then goes away but it's strong enough to stop you in your tracks."* **P17** *"The sort of, most pain with regards to the MS Hug which is around* **15** *the chest, mid rift, it's as though um you are wearing a really tight corset and someone is pulling the strings you know [I: Mm], that's the sort of, that's the most painful side of it."*

3. PAIN BELIEFS	**Pain is unpredictable** This reflects pwMS beliefs about the unpredictability of pain.	**P13** *"It's unexplained, there is no rhyme or reason for it, to be honest sometimes I can be* **75** *sitting there watching the telly and I'll suddenly get these shooting pains up my arm, so yeah it is such a, oh god unpredictable to be honest."* **P20** *"I suppose I don't think about that as much, unless I am really thinking, oh that's really sharp today or and again there is no rhyme or reason as to why it would be worse one day than the next* **274***."* **P6** *"I couldn't tell you, there is no way I could point to a diary and say it is going to happen then [I: Mm] it's just decides um "OK, we are going to do this today" and you just, as I have already mentioned, you do not know until you get up in the morning and you just try and manage your day, from what* **115** *symptoms you have got [I: Mm] at that particular time."* **P24** *"I know everything can change* **55** *within an hour of each other but the beginning of the day it normally – is normally a good representation of how the day will go with me… Or I can be in the middle of a day and I have been fine, all of a sudden the pain will hit, bam, and it's like being – walking straight into a wall."*
	Pain will get worse This reflects pwMS beliefs or ideas about pain getting worse in the future.	**P17** *"Well, I am expecting, I am expecting it because it does, it has got worse, as I say over the past say five or six years, walking distances is more and more difficult so I am imagining that it will get worse and you know, hopefully not too quickly* **110** [coughs] *because my progress has been quite steady, you know quite slow over the years."* **P3** *"I think it will get worse. (I: That's your view is it?) Yes because it has got worse over the last 3 years* **124***."*

		P19 *"I hope I won't get the chronic pain thing that other people get, that does* **255** *worry me [I: Mm] because I know, I have been around others who have, you know, who actually do go through a lot of pain and I don't want to, you know, I don't want to, I think what I go through is more than enough* [laughing] *I am trying not to, hopefully just praying I just don't go that way basically."* **P13** *"I'm not like that, I'm sort of quite a positivity sort of person, so I tend not-, all these people you know they can't get me,* **235** *they make plans for the future, oh you never make any plans, well I don't because I don't know what's gonna happen, you know so I get on with today [I: Mm] and that's, that's my plans for the future really."*
	Personal causal beliefs This reflects pwMS idiosyncratic beliefs about the causes or triggers of their pain.	**P18** *"Yeah, I definitely think that the pain is from the MS because before I was unwell 70, I don't think I really, I didn't really suffer from that much pain and I was able to be quite active and I used to work but um, um, I do definitely think that the pain is due to the MS and it does affect me every day."* **P22** *"I can't be sitting down* [I: Mm] *on my own and then stuck with the pain and then, for me, the pain just gets worse and worse when I am on my own* **223.***"* **P13** *"I'm also taking Ibuprofen and Simvastatin because I've got high cholesterol* **550** *(P: and that's not related to pain though…) well No… having said that, I say no now I since I've been on them I have felt like a 90-year-old lady, and strangely enough I've been on them just over a year when I started to feel worse. Now I'm thinking, and I had forgotten all about this, that it could be related in some way. When I spoke to my next door neighbour*

		who's actually married to a doctor, err he said that he was on them and he's had to come off them because they were making him feel like a 90-year-old man, and he was taking Q10 I think it is, some kind of vitamin because apparently this takes away. So the Jury is out on that one. (I: so are you suggesting that it may be related to your pain in some way?) I'm suggesting it is yeah, maybe related and I have suggested this to my doctor and I had forgotten about it… So I'm taking it, not for pain but for high cholesterol, and it and it may have affected my pain.*"* **P15** *"In my hands, pins and needles, it's kind of quite painful [I: Mm] particularly if it is cold, because even though I have got the pins and needles you would think it would get mottled because it was cold [I: Mm], my hand, they get, it's like a burning pain sensation that I, I do notice that, you know like in your palm [I: Mm], where the fingers are splits into three* **24**.*"* **P2** *"Fluorescent lights in particular disturb my eye, if I get pains after I've been in a room like that I know what's caused it* **111.***"*
4. DEALING WITH FRUSTRATION AND ANGER	**Pains is frustrating and annoying in itself** This reflects pwMS' comments about the pain sensations themselves causing annoyance.	**P4** *"So let's have a think, it's all frustration, um it's why me, um, so I get a bit doomy* **425** *about it."* **P25** *"If I can't go for a walk with my friend, say my friend is walking her dog, and they come, after half an hour, I know I can feel pain increasing, I can feel it travelling up my leg, I can feel the hugging starting, I can feel myself getting upset and cross and then I have to sit down and wait for them [I: Mm], that makes me angry, really angry that I can't and if I dwell on that, if I* **415** *go home and dwell on that, for an hour, while I am waiting for it to recede and if it doesn't recede, then*

		I get more angry and then more upset [I: Yeah, yeah], I try not to because I think, "you are being ridiculous" but I can't stop it." **P12** *"The discomfort causes frustration, so it's just, because it just such weird pain, it's not normal pain a lot of the time [I: Mm], it's just discomfort, like I said before, discomfort leads to frustration, you know when just like the* **350** *hands, 'oh god they are so annoying'. You know when, you know the best way to describe it, you know when something, oh, something is just, it's kind of like a dripping tap or something, it's just like, oh god why is this, just go away kind of thing [I: Mm] that sense of frustration."*
	I can't always do the things I want to do! One of the major elements in this code was the frustration and anger expressed from pain preventing the person doing everyday tasks or meaningful activities.	**P13** *"It just interferes with your life so much, like if somebody says to me, oh do you fancy going to the pub tonight or do you fancy meeting up and go to the restaurant, you have to sort of load yourself up with loads of painkillers and then you don't quite, you know you are not always quite with it [I: Mm] and um yeah I find it really annoying, yeah it is annoying and I do find it very* **220** *frustrating that I'm not able to be like everyone else just to go out and take things for granted, I think is the word [I: Mm] because we all take, I mean everybody, I used to take things for granted, you know, but and now it's just like um, I really have to plan every and I can't adlib and if I do, you know, generally it goes disastrously wrong* [laughing] *[I: Mm] so yeah, I think that's the frustrating bit."* **P25** *"Because I can't do* **400** *what I want to be able to do and it's ridiculous to say to people, um, I have to go one flight of stairs [I: Mm] make a cup of tea, so I can get the lift and I used to, now I try to walk that one flight of stairs and to many people, it would be nothing*

		but sometimes, it feels like an effort that I can't do [I: Mm] and that makes me really cross or really upset [I: Yeah]."
	Pain is annoying because it's always there Comments centre around the pervasiveness of some types of pain relative to others, and how over time this can cause frustration and anger	**P13** *"Okay I got up in the morning, and sometimes I would think, oh I feel fantastic okay I have a woolly leg or a woolly arm or a woolly head even but you know no pain, lovely, and then sort of later on in the evening or in the afternoon, you know you* **175** *start to get these odd shooters or the pins and needles and things which is annoying, aggravating, and they are always there."* **P15** *"I wouldn't wish this on anyone, because the days when, it's just every day the symptoms are becoming annoyance, becoming and then you are doing* **175** *something like getting off a train and you think, oh for god sake when is it going to stop and it isn't going to stop."* **P20** "*Um, it's just there and it bothers me* **25** *because its pain and it's there every day and it's just one of those little things that niggles and it's just, hi, hi I am there, I am still here, you know, just reminding me that I have got MS, I suppose."*
	It makes me grumpy or short-tempered towards others These comments highlight how some pwMS respond to others angrily when experiencing severe pain, or pain which has lasted for long time.	**P15** "*It affects my mood, if I am in a lot of pain, I can get really grumpy [I: Mm, can you tell me why you get grumpy?] If I knew that, I would have a million pounds, I have no idea why I get grumpy when I am in pain, I get really grumpy [I: Mm]* **115** *irritable and to the point where nobody can talk to me because I am so ahhhhhhh leave me alone [I: Mm] and then let them know everything is painful, I feel guilty about it afterward but at the time I am in pain, leave me alone, I have to deal with it, I can go and chill out and you know."* **P5** *"It's not very nice for people* ***192*** *around you when you know, like my*

		kids or my wife, like one day I've got my grumps on and it's like, 'What have you got the hump for?', 'I've not got the hump I'm just in pain and it won't go away." **P14** *"Going out in this weather, I want to do something, I want to take my mother for lunch say but that involved going out in the heat, getting in a car, driving, helping her and stuff and I know if I did that I'd be exhausted [I: Mm] by the time I got there and then I'd start to feel uncomfortable and then pain would generally, or discomfort, would generally start in my right foot* **180** *and travel up and then you tend to get a little short tempered because it's very unfair for other people so if I didn't go out into the heat and I didn't do that, then I wouldn't have to suffer that and nor would anybody else, so that's what I mean about behaving badly, you have just got to control your life and do what the things you can do and not make it worse*."
5. ATTITUDES & BELIEFS ABOUT MANAGEMENT	**I've tried most things and it's a case of hit and miss** This subtheme attempts to capture the seemingly vast list of strategies used by pwMS to their manage pain. Whilst pwMS suggested some strategies were effective, they also indicated that other times they were not. This also includes comments about using strategies even when the person knows they are ineffective.	**P18** *"Um, I don't think that they are great but it just* **180**, *I think that it's mostly for comfort [I: Okay] because it doesn't really take away the pain, it just makes me feel a bit better, like even with paracetamol or Nurofen, I don't think it helps at all."* **P24** "*I have also used cold packs. You can put them – you put them in the freezer and you can use them again and again and again and you can strap them* **455** *to an area of your body that's the painful area and that tends to work as well. I think it's like different stimulations will affect different kinds of pain or different areas…* *… The least effective thing* **466** *… would be – the least effective thing – oh, the least effective thing for me was my TENS machine…*

		…Um, I have tried some herbal remedies. Doesn't help. I have had acupuncture. [Laughter] That doesn't help either **228**." **P9** "*Um, mindfulness doesn't eliminate it* **310,** *but it does make it more bearable, so yeah from that point of view it is helping*." **P18** *"If it's like pains that feel like they are in my muscle or deep in my bones, I use um like hot water bottles or um paracetamol or the heat, you know the heat rub [I: Yes] I don't usually use, I never usually use ice [I: Do you mean Deep Heat?] yeah."* **P10** "*I did try reflexology for a while* **405**, *I know some people love it but I didn't find I got any benefit from it at all. It's nice to have and it makes you relax for a while [I: Mm] but it didn't actually help any pain that I was having."* **P6** "*I have tried all these things that I have already mentioned, and I tried, tried and tried and nothing has really worked"* **160**.
	Common ways pwMS self-manage pain This reflects pwMS frequently expressed a tendency to either rest excessively or over-exert themselves when experiencing pain. This includes comments about the ills of doing either. It also includes taking pain medications.	**P17** "*I think the thing that makes pain worse is certainly over doing it, it is you know, over doing, whatever you are doing, today we came home yesterday, and the reason I didn't go to bed last night and I am not going to work today but I did* **150** *cut the grass, I went out and cut the grass [I: Mm] I have got a petrol driven mower which has got, which has got gears so it's um, I don't have to actually physically push it [I: Mm], I just walk behind it and keep it in line, you know [I: Yeah] but I cut the grass and then I will be absolutely exhausted after that."* **P9** "*So instantly being able go and garden all day like I used to be able to do, um, I know I can do it for, I*

		can do **110** *it okay for ten minutes without problems, if I do it for half an hour, um, I am on my hands and knees coming back into the house and then I have to lay down for a couple of hours."* **P12** *"Well if it is really bad, I just stay in bed and I rest, you know and if I, and* **185** *also if I haven't had a good night's sleep, because if you, if the pain is going through the sleep, then obviously in the morning I'm like, well you know I think it is best if I just stay home and rest."* **P14** *"I'm a long-termer with this* **295** *so, it, it's just is, if that makes any sense, it's there [I: Mm], I know it's going to be there, if it's a good day it's not going to be there, good day I do a lot more, a bad day I do a lot less."* **P2** "*I had to rest my right-eye* [optic neuritis] **147** *and rest in general really because the neurologist said I needed to get the inflammation down."* **P12** "*I'm going to maybe take some ibuprofen or something or whatever and just try* **170** *and deal with it."* **P25** "*I do take different drugs for it,* **135** *um so I take quite a high dose of Pregabalin [I: Mm] with Amitriptyline."* **P23** *"Yeah, I think it is* working [pain medications], *it's working. I'm not feeling too much pain. It must be working, it must be* **78***."*
	Pain reduction agenda This incorporates talking about fighting or battling with pain, engaging in fighting talk, and their efforts to	**P5** "*Find me wonder drug… I, I don't care what it is, how it works but find* **555** *me a wonder drug that will take the pain away enough that I can function without taking a handful of tablets all the time."* **P15** "*Just relief from the pain I have, so I don't have it anymore, or*

	reduce or control pain. Some pwMS recited long lists of strategies they continue to use with little effect (see subtheme: *I've tried most things and it's a case of hit and miss*).	*if I do, that it's* **570** *less than what I have been experiencing [I: Mm] that has to be the ultimate goal, I can't think of anything else, if I was, if I was going to do something for pain, I would want the pain to be less or non-existent [I: Mm] it has to be."* **P25** "*I don't really have that toolkit of like pain* **680** *relieving mechanisms in my brain to do that [I: Yeah], that would be really good."* **P1** "*If I can find a drug* **135** *that nobody else has had I'll get it."* **P8** "*Um what I think I try and do is I try and take proper painkillers and if that doesn't work then I try something, rather than just giving up, so I would have something to eat to see it that might help, I might have something to drink to see* **355** *if that might help."*
	Managing and accepting agenda Some pwMS described pain as incurable, and described a different approach to managing pain that did not involve trying to reduce or control it. Rather greater emphasis was placed on being open to the idea that pain will come and go, and make room for it in one's life.	**P6** *"Unfortunately the pain I am getting now, um is not, incurable [I: Mm] um, it will not go away completely"* **145**. **P14** *"Specifically, it limits me doing things I want to do at times, but I will do, there's a way of doing everything I want to do, I just have to organise my life and think about it, so if I want to go out to dinner with my husband and it's a company do or something like that, then I'm not going to be able to go out the night before or the night after, and probably not for the next two day, so I will* **205** *rest for two days, just to do that one event, so if I can control my life, then, then things work out well."* **P13** *"Because we all take, I mean everybody* **220***, I used to take things for granted, you know, but and now it's just like um, I really have to plan every day, and I can't ad-lib and if I do, you know, generally it goes*

		disastrously wrong ((laughing)) [I: Mm] so yeah, I think that's the frustrating bit." **P24** "*What is – my view on pain is, it's* **180***– some of it you can work through [I: Hmm]. And there is certain pains you can work through, which – I have three – two classes of pain: a secondary pain and a predominant pain. My secondary pain I can work through on day-to-day things. Even though I am in pain today [I: Mm mm]. I will still do various bits and pieces that I need to do. [I: Yeah]. Because it has to be done. In the house, I must 185stress this, in the house or when it's nicer and warmer I will go in the garden and do my flowers and do the roses blah, blah, blah and I will just work through it. And it helps sometimes to do that. [I: Yeah]. But on the other side of it, when I have predominant pain it is excruciating and I know I cannot push myself through that. [I: Hm]. I just – there are some days it's like with the MS, you just* **190** *go with it, you have to. You can't fight it; you just go with it. [I: Hm]. And that is my – um, when I talk to a friend of mine about her problems, I say to her well, you know, today is one of the days you can't work through it, you have just got to go with it. So – because we – we're not these kind of defeatist people, we like to you know, just hold our own, you know but you* **195** *can't… I am very determined but I am a realist and I know when to fight it and when not to fight it."* **P7** *"I have got the referral to the pain* **295***management clinic and I suppose until I have heard what there is out there and, you know, if there is anything that will promote me in managing my pain, you know, my – my belief at the moment is – is that I don't – I think it is just there. And I will have to adapt to leading*

		my life with it there." **P12** "*Um, right okay, what would I expect the outcome to be? [I: Yeah, what would you expect, sorry] being able to cope, but the thing is you can't cure it can you, that's the thing, so it is all about management… And managing yourself [I: Right] and knowing what medications to take at* **565** *what time and these, it is, a lot of it is management [I: Mm] pain management rather than pain curing."*
	Catch-22 This reflects comments about the cycle or 'roundabout' of pain's interaction with other symptoms (usually pain and fatigue) and its impact on behaviour. Usually there is a focus on trying to avoid pain, which inadvertently creates problematic cycles. Individuals can experience their own unique catch-22 cycle (e.g. weight gain, fatigue, mobility etc.).	**P12** *"I think it does, I think it does, I think stress, all these things, there another thing I could of added with diet, you know, diet, exercise, sleep and stress is a major one [I: Mm] you know and le- you know, because it's a brain related illness, I think that you* **605** *have to not let your, not let yourself get wound about things in your head because, you know it's like, it's like a, what's the word I'm, what do they call it, a circle, you know it's like you are getting pain, and then you get stressed about the pain and then the stress causes the pain to get worse [I: Mm] and again that goes back to management as well, a vicious circle, that's what I'm thinking of, you know the* **610** *saying, a vicious circle you know you get the pain, you get the stress and then you get more pain, you know you've got to break the circle, you've got to say to yourself, right I have got some pain, I've got to cope with this and I have to not let it stress me out, I have to go and sit in a cool bath or something, take myself away from everything, you know."* **P13** *"Um yeah, well the sitting down thing for too long* **533** *obviously it just hurts my back too much, so um I have to move around, but in moving around I tire myself out, or then the MS kicks-in, so it is a little bit of a*

		catch-22 there. Um, but yeah I have to say it is one of these things that um unfortunately because I put on a lot of weight recently I think my MS has got worse, I've actually put on loads of weight because I can't do much to get rid of it. And even though I don't eat too much I'm obviously not burning up the calories, so that is a problem at the moment. And as I was told by the neurologist when I was first diagnosed carrying the weight doesn't help the legs. So again I'm in like a little circle here, it's really hard. I mean I have cut down on my eating, I've actually lost half a stone, but it took months, months it's taken me to lose it. Um, and it's an ongoing thing that I keep off the chocolate and the puddings and the sweets and everything else. Um but I have to do it (I: it's all part of this isn't it?) Well yeah this is it, so it is a catch-22 and that's the way as well." **P17** *"There are other things they prescribe for, um, for MS Hug which is like, like the Gabapentin or Amitriptyline, those drugs [I: Mm] which do help but unfortunately they also have side effects [I: Mm] and the side effects are, ((chuckles)) they keep you more tired and when, and when that* **100** *is a major factor in suffering with MS, you tend to think, well I don't really want to take that because I know how it's going to make me feel so, you sort of suffer in one pain to get rid of another, you know."*
	Fighting Talk This subtheme highlights the tendency for some pwMS to vocalise their frustration with pain and MS, and describe going into battle or fighting	**P21** *"Um, with that, it is definitely, just because I am a fighter in terms of like, I don't dwell on the fact that I have MS, I try and get on with it [I: Mm] so when I do get pain, it is really awkward for me because I want to continue my day, I feel* **25** *like I have been slowed down, I feel like I have been defeated so I tend to just try and get on with it, so it's*

	with it, or and feeling defeated.	*awkward for me."* **P6** "*I don't like that idea at all, that is to me the worse consequence and unfortunately I mustn't think about it because that is what really, I'm a fighter and I will fight as much as I can, now* **270** *once I can't and that doesn't bear thinking about."* **P25** "*Because, I am not good at resting, I hate it, I hate the fact that I have to rest, I find it depressing [I: Mm], that makes me want to cry, just the, just talking to you thinking about it, I hate, um so probably I battle it and actually I was just saying to a friend, "I just feel I am in a fight all the time, with myself" [I: Mm] "and my work!" [I: Yeah],* **470** *sorry I seem to be talking about work quite a lot but [I: No, it makes sense], that's where it impacts in my life the most [I: Yeah], I have to pretend [I: Mm] and if I could just like allow myself, I don't know, I don't know if it is a good thing that I fight it or a bad thing."*

6. AN INVISIBLE EXPERIENCE PRECLUDING UNDERSTANDING	**Pain and MS is Invisible to Others** Comments where pwMS highlight that others fail to see, or are blind, to the invisible nature of pain and MS.	**P2** *"Because it's something people can't see... You know, somebody's walking around with an arm in a sling or plaster* **305** *on their arm or leg people go oh you've broken your leg."* **P10** *"I think it is quite difficult for people* **331***, unless you are actually in a wheelchair or permanently on walking sticks, they say "oh you are looking really well today!"* **P12** "*Can I give you an example of, well like I said it is just people not understanding and people looking at me funny because I've got a glove on, you know, when I'm like walking* **425** *slowly or something, people are like, why are you walking so slowly, people just not being very understanding but I think they, I think they've become more understanding [I: Mm] over the years um but when I first had it, people were a bit like, what is there really anything-, what on earth is wrong with you? I think that's the big thing with MS, it's not a very visible disease."* **P17** "*Because it isn't visible, you know, I find that most people will look at me and see, and don't really think there is anything wrong with me, because there's you* **245** *know, there's nothing, there is nothing visible as far as MS is concerned and because um it's such a, what's the word, it's, the disease is so diverse that symptoms change regularly."*

	Concealing and not Revealing Comments mostly about preserving relationships and protecting oneself from the well-intentioned, but often disempowering, actions and stigma from others by concealing the experience of pain from others. This can include being overly solicitous.	**P3 "***You can't keep on moaning to people [pain], because, well, they wouldn't come and see you anymore would they* **102***?"* **P18** "*Um, I am not too sure because um when I do experience pain and I have been* **295** *unwell, I don't really go out and I don't think I am open with my MS or my pain in this, I am quite close to the person, it's not something that I really, that I would tell anybody else, unless I have a good relationship with, like I don't really open up about it?* (Crying) [*I: May I ask why that might be, from your perspective?] P: Um, I am not sure, I didn't think it was deliberate, um I don't know why [I:* **310** *Mm] I haven't really thought about it."* **P8** "*Um, I don't actually let on very much actually, it's only my kids that know I* **370** *am in pain, um and my husband, other than that I don't let it on."* **P1** "*If you're just standing there talking to them [I: Mm] they don't recognise that you're ill [I: Yeah]. Err, and thank God for it! I do, I-I-I think it's a good thing for your self-esteem. Um, and the fact that you're able to* 255 *carry off, particularly doing what I'm doing, you're able to at least be taken as somebody who is still in their right mind."* **P25** "*I kind of pretend and that makes me feel sad, I feel quite angry, I fluctuate between feeling really pissed off and angry [I: Mm] feeling really upset and kind of teary, I* **400** *used to feel really teary at work a lot [I: What's the nature... sorry] but I could, sorry, but I would quite easily feel teary tomorrow."*
	Feeling alone with the embodied experience of pain and MS	**P3** "*That's right, 'cause I mean pain is very, um, what can I say it's sort of like to you alone, you know what pain you're in*."

	Comments around other people (family and friends) never fully understanding the nature and extent of pain and MS, which can feel isolating. In addition, describing it to others is felt by some to be a rather limited way to convey their pain experience.	**P13** *"I don't think you can ever, ever, ever describe a pain that you are feeling to anyone else and I don't think, unless other people are in the same position as you* **110** *and experiencing the pain, nobody can understand it, nobody. There is nobody out there that, I mean I can whinge to my sons or my friends and say, oh god you know I've had such an awful-, now funnily enough my friend who has had a stroke can actually empathise, yeah, just you know he understands where I'm coming from now, because he actually gets very, very similar things."* **P15** "*I now see, pain and people differently, because I am a civil servant and if somebody was to say to me, I am in chronic pain but I want to work, I would more look at it and think, I can kind of understand what you mean [I: Mm] because I have experienced it [I: Mm] rather thinking, I will just take a tablet, you know what I mean [I: Yeah] and you know* **170** *they say, you have a walk a mile in somebody's shoes before you can understand, I wouldn't want anyone to walk in my shoes [I: Mm] because ((chuckles)) I don't think I could walk a mile but two, it's not nice [I: Yeah], it's not, I wouldn't wish this on anyone.* **P18** *"Even if I describe my pain [I: Mm] it's, it's, I know that, it would take a while for those people to understand how I am describing it [I: Yeah] because it's not something that they get [I: Right] do you understand how I* **145** *mean*?" **P21** *"I am just thinking, um, I might watch a DVD, there is not much that I would do really because I just think sometimes that just the day for me to rest [I: Yeah] it's* **335** *just my body saying, "you know what, I*

		think I have done my part and I just rest for a bit and then we can get back to doing it how you want to", that's how I just speak to myself like that [I: Mm], but um [I: So some self-talk going on?] Yeah! [I: Yeah] It helps me because, I mean, yeah it helps because I am the only one who understands me [I: Mm] so, or even understands what I am going **340** *through in terms of how I feel today"* **P7** *"It feels like there is something – what I* **80** *said to a friend of mine last week, touch my hand, just feel how odd they feel, and of course you can't. You know, because only I can feel it inside my body*."

Appendix F. Chapter 5 Cross-sectional Study: Hierarchical Regression Sensitivity Analyses Examining Psychosocial Predictors of Pain Severity (*n*=567) and Pain Interference (*n*=568) (BPI) after Removing Anxiety and Depression (HADS)

	Pain Severity			Pain Interference		
	Beta	**p**	**ΔR^2**	**Beta**	**p**	**ΔR^2**
Step 1: Demographic and disease variables			.19 (F=14.638, p<.001)			.27 (F = 22.297, p<0.001)
			95% CIs			**95% CIs**
Age	-.125	.004	-.042 to -.008	-.224	<.001	-.071 to -.033
Gender	.049	.213	-.139 to .619	.069	.065	-.025 to .825
Employment status	.089	.049	.002 to .813	.163	<.001	.427 to 1.337
RRMS (Ref) vs SPMS subtype	.028	.521	-.286 to .564	.063	.136	-.114 to .841
RRMS (Ref) vs PPMS subtype	-.008	.876	-.518 to .442	-.010	.834	-.597 to .482
No current relapse (Ref) vs Current relapse	.089	.025	.065 to .982	.126	.001	.360 to 1.390
No current relapse (Ref) vs Not applicable	.048	.299	-.220 to .716	.032	.468	-.331 to .720
Mobility (EDSS-S)	.269	<.001	.307 to .620	.329	<.001	.493 to .844
Pain type (S-LANSS)	.262	<.001	.811 to 1.492	.211	<.001	.709 to 1.473

BPI: Brief Pain Inventory; Ref: Reference group; Beta: Standardized Coefficients; ΔR^2: R-squared change; Overall R^2: Total effect in regression model; p: 95% significance value; NS: Non-significant parameters; 95% CIs: 95% Confidence Intervals for standardised Beta.
Demographic and disease variables: Employment status: Employed vs unemployed; EDSS-S: Self-report Expanded Disability Status Scale; HADS: Hospital Anxiety and Depression Scale; PPMS: primary progressive multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.
Psychosocial predictors: AEQ: Avoidance-Endurance Questionnaire; CFQ: Cognitive Fusion Questionnaire; CPAQ: Chronic Pain Acceptance Questionnaire; IPQ-R: Illness Perceptions Questionnaire; PCS: Pain Catastrophizing Scale
Pain outcomes: BPI: Brief Pain Inventory Short Form; S-LANSS: Self-report Leeds Assessment of Neuropathic Signs and Symptoms.

	Pain Severity			Pain Interference		
	Beta	**p**	**ΔR^2**	**Beta**	**p**	**ΔR^2**
Step 2: Psychosocial factors			.23			.28
			(F=20.35, p< 0.001)			(F=31.77, p< 0.001)
			95% CIs			**95% CIs**
Cognitive fusion **(**CFQ)	-.105	.013	-.038 to -.005	-.003	.928	-.018 to .017
Pain acceptance **(**CPAQ)	.053	.331	-.014 to .040	-.012	.808	-.032 to .025
Avoidance of social activities (AEQ)	.073	.132	-.035 to .263	.161	<.001	.142 to .453
Avoidance of physical activities (AEQ)	-.038	.389	-.215 to .084	-.034	.389	-.225 to .088
Behavioural endurance (AEQ)	.134	<.001	.150 to .517	.076	.022	.033 to .415
Pain catastrophizing (PCS)	.225	<.001	.024 to .060	.166	<.001	.018 to .055
Timeline (IPQ-R)	.260	<.001	.079 to .147	.095	.007	.014 to .084
Timeline-cyclical (IPQ-R)	-.074	.042	-.084 to -.002	.012	.714	-.035 to .051
Consequences (IPQ-R)	.209	<.001	.051 to .131	.354	<.001	.139 to .223
Personal control (IPQ-R)	-.053	.146	-.056 to .008	-.056	.081	-.063 to .004
Coherence (IPQ-R)	-.075	.027	-.059 to -.004	-.013	.674	-.035 to .023
		Overall R^2=.42			**Overall R^2** =.55	
		(F=20.30, p< 0.001)			(F=33.59, p<.001)	

BPI: Brief Pain Inventory; Ref: Reference group; Beta: Standardized Coefficients; ΔR^2: R-squared change; Overall R^2: Total effect in regression model; p: 95% significance value; NS: Non-significant parameters; 95% CIs: 95% Confidence Intervals for standardised Beta.
Demographic and disease variables: Employment status: Employed vs unemployed; EDSS-S: Self-report Expanded Disability Status Scale; HADS: Hospital Anxiety and Depression Scale; PPMS: primary progressive multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.
Psychosocial predictors: AEQ: Avoidance-Endurance Questionnaire; CFQ: Cognitive Fusion Questionnaire; CPAQ: Chronic Pain Acceptance Questionnaire; IPQ-R: Illness Perceptions Questionnaire; PCS: Pain Catastrophizing Scale
Pain outcomes: BPI: Brief Pain Inventory Short Form; S-LANSS: Self-report Leeds Assessment of Neuropathic Signs and Symptoms.

Appendix G. Chapter 5 Cross-sectional Study: Third Step of the Hierarchical Regressions Including Pain Subtype and Psychosocial Predictor Interaction Terms of Pain Severity (n=567) and Pain Interference (n=568) (BPI)

	Pain Severity			Pain Interference		
Step 3: All psychosocial factors and pain type (S-LANSS) interaction terms	**Beta**	**p**	**ΔR^2**	**Beta**	**p**	**ΔR^2**
			.008 (F=.655, p= .794)			.004 (F=.436, p= .949)
			95% CIs			**95% CIs**
Anxiety and depression (HADS) x S-LANSS	-.049	.562	-.84 to 0.46	.004	.957	-.065 to .069
Cognitive fusion (CFQ) x S-LANSS	.069	.365	-.021 to 0.56	-.025	.711	-.047 to .032
Pain acceptance (CPAQ) x S-LANSS	-.056	.516	-.075 to .038	.050	.506	-.038 to 0.078
Avoidance of social activities (AEQ) x S-LANSS	-.098	.209	-518 to .114	-.034	.614	-.408 to .241
Avoidance of physical activities (AEQ) x S-LANSS	-.005	.942	-314 to .291	-.018	.750	-361 to .260
Behavioural endurance (AEQ) x S-LANSS	.035	.536	-.254 to .487	.035	.477	-.243 to .518
Pain catastrophizing (PCS) x S-LANSS	.015	.865	-.036 to .043	.056	.449	-.025 to .056
Timeline (IPQ-R) x S-LANSS	-.079	.183	-.116 to .022	.036	.485	-.088 to .055
Timeline-cyclical (IPQ-R) x S-LANSS	.017	.772	-.073 to 0.098	-.023	.648	-.056 to .119
Consequences (IPQ-R) x S-LANSS	.051	.454	-.051 to .114	.029	.633	-.064 to .105
Personal control (IPQ-R) x S-LANSS	-.078	.175	-.112 to .020	-.007	.892	-.072 to .063
Coherence (IPQ-R) x S-LANSS	-.047	.437	-.084 to 0.36	-.043	.416	-.087 to .036

BPI: Brief Pain Inventory; Ref: Reference group; Beta: Standardized Coefficients; ΔR^2: R-squared change; Overall R^2: Total effect in regression model; p: 95% significance value; NS: Non-significant parameters; 95% CIs: 95% Confidence Intervals for standardised Beta.
Demographic and disease variables: Employment status: Employed vs unemployed; EDSS-S: Self-report Expanded Disability Status Scale; HADS: Hospital Anxiety and Depression Scale; PPMS: primary progressive multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.
Psychosocial predictors: AEQ: Avoidance-Endurance Questionnaire; CFQ: Cognitive Fusion Questionnaire; CPAQ: Chronic Pain Acceptance Questionnaire; IPQ-R: Illness Perceptions Questionnaire; PCS: Pain Catastrophizing Scale
Pain outcomes: BPI: Brief Pain Inventory Short Form; S-LANSS: Self-report Leeds Assessment of Neuropathic Signs and Symptoms.

Appendix H. Chapter 5 Cross-sectional Study: Hierarchical Regression Subgroup Analyses Examining Psychosocial Predictors of Pain Severity and Pain Interference (BPI) in PwMS with Neuropathic Pain (*n*=342)

	Pain Severity			Pain Interference		
	Beta	**p**	**ΔR^2**	**Beta**	**p**	**ΔR^2**
Step 1: Demographic and disease variables			.16 (F=7.72, p<.001)			.27 (F=15.22, p<0.001)
			95% CIs			**95% CIs**
Age	-.220	<.001	-.066 to -.022	-.290	<.001	-.090 to -.043
Gender	.041	.429	-.321 to .753	.103	.033	.051 to 1.199
Employment status	.085	.145	-.132 to .896	.148	.007	.211 to 1.310
RRMS (Ref) vs SPMS subtype	.062	.282	-.235 to .806	.081	.129	-.126 to .986
RRMS (Ref) vs PPMS subtype	.028	.671	-.519 to .805	-.008	.897	-.754 to .661
No current relapse (Ref) vs Current relapse	.118	.024	.083 to 1.203	.162	.001	.410 to 1.607
No current relapse (Ref) vs Not applicable	.113	.060	-.025 to 1.258	.059	.295	-.320 to 1.051
Mobility (EDSS-S)	.306	<.001	.328 to .740	.399	<.001	.578 to 1.018

BPI: Brief Pain Inventory; Ref: Reference group; Beta: Standardized Coefficients; ΔR^2: R-squared change; Overall R^2: Total effect in regression model; p: 95% significance value; NS: Non-significant parameters; 95% CIs: 95% Confidence Intervals for standardised Beta.
Demographic and disease variables: Employment status: Employed vs unemployed; EDSS-S: Self-report Expanded Disability Status Scale; HADS: Hospital Anxiety and Depression Scale; PPMS: primary progressive multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.
Psychosocial predictors: AEQ: Avoidance-Endurance Questionnaire; CFQ: Cognitive Fusion Questionnaire; CPAQ: Chronic Pain Acceptance Questionnaire; IPQ-R: Illness Perceptions Questionnaire; PCS: Pain Catastrophizing Scale
Pain outcomes: BPI: Brief Pain Inventory Short Form; S-LANSS: Self-report Leeds Assessment of Neuropathic Signs and Symptoms.

	Pain Severity			Pain Interference		
	Beta	**p**	**ΔR^2**	**Beta**	**p**	**ΔR^2**
Step 2: Psychosocial factors			.20			.25
			(F=8.32, p <0.001)			(F=14.21, p< 0.001)
			95% CIs			**95% CIs**
Anxiety and depression (HADS)	.067	.343	-.021 to .061	.209	.001	.031 to .113
Cognitive fusion **(**CFQ)	-.122	.067	-.050 to .002	-.116	.044	-.052 to -.001
Pain acceptance **(**CPAQ)	.046	.535	-.025 to .049	.037	.563	-.026 to .047
Avoidance of social activities (AEQ)	-.008	.906	-.244 to .198	.095	.104	-.036 to .382
Avoidance of physical activities (AEQ)	-.017	.783	-.250 to .189	-.019	.728	-.256 to .179
Behavioural endurance (AEQ)	.137	.012	.079 to .618	.073	.117	-.053 to .480
Pain catastrophizing (PCS)	.224	.001	.017 to .064	.161	.005	.010 to .057
Timeline (IPQ-R)	.186	.001	.035 to .136	.059	.221	-.019 to .080
Timeline-cyclical (IPQ-R)	-.064	.226	-.093 to .022	.024	.603	-.042 to .072
Consequences (IPQ-R)	.213	.001	.041 to .160	.354	<.001	.134 to .251
Personal control (IPQ-R)	-.092	.078	-.086 to .005	-.073	.103	-.082 to .008
Coherence (IPQ-R)	-.093	.054	-.073 to .001	-.027	.515	-.049 to .024
		Overall R^2=.36			**Overall R^2** =.52	
		(F=8.9, p<.001)			(F=17.51, p<.001)	

BPI: Brief Pain Inventory; Ref: Reference group; Beta: Standardized Coefficients; ΔR^2: R-squared change; Overall R^2: Total effect in regression model; p: 95% significance value; NS: Non-significant parameters; 95% CIs: 95% Confidence Intervals for standardised Beta.
Demographic and disease variables: Employment status: Employed vs unemployed; EDSS-S: Self-report Expanded Disability Status Scale; HADS: Hospital Anxiety and Depression Scale; PPMS: primary progressive multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.
Psychosocial predictors: AEQ: Avoidance-Endurance Questionnaire; CFQ: Cognitive Fusion Questionnaire; CPAQ: Chronic Pain Acceptance Questionnaire; IPQ-R: Illness Perceptions Questionnaire; PCS: Pain Catastrophizing Scale
Pain outcomes: BPI: Brief Pain Inventory Short Form; S-LANSS: Self-report Leeds Assessment of Neuropathic Signs and Symptoms.

Appendix I. Chapter 5 Cross-sectional Study: Hierarchical Regression Subgroup Analyses Examining Psychosocial Predictors of Pain Severity and Pain Interference (BPI) in PwMS with Non-Neuropathic Pain (*n*=225)

	Pain Severity			Pain Interference		
	Beta	**p**	**ΔR^2**	**Beta**	**p**	**ΔR^2**
Step 1: Demographic and disease variables			.09 (F=2.75 p=0.006)			.15 (F=4.61, p< 0.001)
			95% CIs			**95% CIs**
Age	.029	.705	-.021 to .031	-.149	.047	-.064 to <.001
Gender	.046	.498	-.361 to .740	.023	.720	-.550 to .794
Employment status	.102	.200	-.230 to 1.092	.204	.008	.281 to 1.888
RRMS (Ref) vs SPMS subtype	-.049	.527	-.980 to .504	.023	.764	-.767 to 1.043
RRMS (Ref) vs PPMS subtype	-.103	.245	1.130 to .290	-.034	.688	-.1042 to .689
No current relapse (Ref) vs Current relapse	.055	.412	-.470 to 1.144	.072	.268	-.430 to 1.538
No current relapse (Ref) vs Not applicable	-.034	.680	-.855 to .558	-.010	.898	-918 to .806
Mobility (EDSS-S)	.254	.002	.142 to .625	<.001	.001	.210 to .799

BPI: Brief Pain Inventory; Ref: Reference group; Beta: Standardized Coefficients; ΔR^2: R-squared change; Overall R^2: Total effect in regression model; p: 95% significance value; NS: Non-significant parameters; 95% CIs: 95% Confidence Intervals for standardised Beta.
Demographic and disease variables: Employment status: Employed vs unemployed; EDSS-S: Self-report Expanded Disability Status Scale; HADS: Hospital Anxiety and Depression Scale; PPMS: primary progressive multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.
Psychosocial predictors: AEQ: Avoidance-Endurance Questionnaire; CFQ: Cognitive Fusion Questionnaire; CPAQ: Chronic Pain Acceptance Questionnaire; IPQ-R: Illness Perceptions Questionnaire; PCS: Pain Catastrophizing Scale
Pain outcomes: BPI: Brief Pain Inventory Short Form; S-LANSS: Self-report Leeds Assessment of Neuropathic Signs and Symptoms.

	Pain Severity			Pain Interference		
	Beta	**p**	**ΔR^2**	**Beta**	**p**	**ΔR^2**
Step 2: Psychosocial factors			.36			.44
			(F=11.37, p< 0.001)			(F=18.16, p< 0.001)
			95% CIs			**95% CIs**
Anxiety and depression (HADS)	.162	.063	-.063 to -.003	.169	.025	.117 to .357
Cognitive fusion **(**CFQ)	-.229	.003	.003 to -.073	-.053	.424	.019 to .458
Pain acceptance **(**CPAQ)	.134	.148	.148 to -.011	-.015	.489	.041 to .313
Avoidance of social activities (AEQ)	.173	.039	.039 to .013	.190	.009	.583 to .384
Avoidance of physical activities (AEQ)	-.007	.921	-.921 to .219	-.001	.987	.226 to .493
Behavioural endurance (AEQ)	.133	.027	.027 to .033	.054	.300	.426 to .744
Pain catastrophizing (PCS)	.179	.030	.030 to .003	.081	.259	.052 to .395
Timeline (IPQ-R)	.355	<.001	<.001 to .084	.086	.128	.091 to .640
Timeline-cyclical (IPQ-R)	-.099	.086	.086 to -.116	-.015	.770	.057 to .818
Consequences (IPQ-R)	.218	.006	.006 to .023	.389	<.001	.241 to .443
Personal control (IPQ-R)	.001	.990	.990 to -.046	-.058	.249	.021 to .802
Coherence (IPQ-R)	-.017	.759	.759 to -.052	.045	.359	.073 to .850
		Overall R^2=.45			**Overall R^2** =.59	
		(F=8.565, p<.001)			(F=14.502, p<.001)	

BPI: Brief Pain Inventory; Ref: Reference group; Beta: Standardized Coefficients; ΔR^2: R-squared change; Overall R^2: Total effect in regression model; p: 95% significance value; NS: Non-significant parameters; 95% CIs: 95% Confidence Intervals for standardised Beta.
Demographic and disease variables: Employment status: Employed vs unemployed; EDSS-S: Self-report Expanded Disability Status Scale; HADS: Hospital Anxiety and Depression Scale; PPMS: primary progressive multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.
Psychosocial predictors: AEQ: Avoidance-Endurance Questionnaire; CFQ: Cognitive Fusion Questionnaire; CPAQ: Chronic Pain Acceptance Questionnaire; IPQ-R: Illness Perceptions Questionnaire; PCS: Pain Catastrophizing Scale
Pain outcomes: BPI: Brief Pain Inventory Short Form; S-LANSS: Self-report Leeds Assessment of Neuropathic Signs and Symptoms.

INFORMATION SHEET FOR PARTICIPANTS

KING'S College LONDON
University of London

REC Reference Number: 13/LO/1429

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET
Pain Experience in MS (PEMS) Study

You are being invited to take part in a research study. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with family members or friends if you wish. Please contact me if anything is unclear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

Who is conducting the study?
This study is part of a larger research project that is being conducted by researchers at The Section of Health Psychology, Institute of Psychiatry at King's College in collaboration with the MS Society UK. The study is being conducted as part of the Principal Investigator (Anthony Harrison's) doctoral studies in conjunction with Lead Investigators Professor Rona Moss-Morris and Professor Lance McCracken. Anthony is being supervised by the Lead Investigators with all aspects of the project.

What is the purpose of the study?
Research has shown that people with MS experience different kinds of pain, but there is little research into how this symptom is experienced by people with MS. We are interested in how people with MS experience their pain, how much it affects them, and how they deal with it from the day-to-day. Understanding how people with MS live from the day-to-day with different kinds of pain will help researchers develop new treatments aiming to improve how people with MS deal with their pain.

Why have I been chosen?
You have been approached about this study because you have Multiple Sclerosis and have reported to us that you experience some form of pain. We have invited those people with a variety of MS pain symptoms to take part in the project.

Do I have to take part?
No. It is up to you to decide whether to take part or not. If you decide to take part you will be asked to sign the consent form provided. Whether or not you take part will not affect the standard of care you receive. If you agree to take part you may be asked whether you are happy to be contacted about participation in future studies. However, your participation in this study will not be affected should you request not to be re-contacted.

What will happen to me if I take part?
If you agree to take part you can either access the online questionnaire directly: https://www.survey.bris.ac.uk/kcl.pemsstudy. Alternatively, a member of the research team will contact you using the contact details you provide. They will arrange to send you either a paper-version of the questionnaire survey or web-link to access the online version. The questionnaires should take around 20-30 minutes to complete. The research team is in no way connected with the team involved in your treatment. The survey will ask you some standard questions about how you view your pain, how it affects your life, how you deal with pain alongside other more general difficulties.

Will You Compensate Me for My Time?
We would very much appreciate your help and to express our thanks for your time completing the survey we will offer you a £5 *Marks & Spencer's* gift voucher, which we can give to you at your appointment or post to your home address if you prefer. At the conclusion of the study, we will also provide you with a newsletter summarising the main findings.

Are there any costs?
There are no costs to participants associated with the project.

What are the possible disadvantages and risks of taking part?
The risks involved in participating are minimal. It is possible that some people might find it distressing to reflecting on the questions in relation to their own lived experiences of pain and MS in general. If you get upset you can skip questions, take a break or decide not to continue with the survey. If you are very distressed we will offer you some sources of support.

What are the possible benefits of taking part?
There may not be any immediate or direct benefits to you by taking part. However, some people may find it helpful or interesting to talk about their illness and how it affects them. Your participation will help us to develop a better idea of how we can help people who experience MS pain. At the conclusion of the project, we will send you a newsletter describing the major findings and alerting you to any research publications we have generated from the project.

If this study has harmed you in any way…
In the unlikely event that you are unhappy with the way that the research is conducted complaint mechanisms are available to you. In the first instance please contact Professor Rona Moss-Morris rona.moss-morris@kcl.ac.uk. If you are not satisfied with this process, we advise you contact the Patient Advice and Liaison Service (PALS), at **Guy's and St. Thomas' Hospital's PALS** KIC Ground floor, North Wing, St Thomas' Hospital, Westminster Bridge Road London SE1 7EH (tel. 0207 1888801 or 0207 1888803 or email pals@gstt.nhs.uk). **Kings College Hospital PALS,** King's College Hospital, Denmark Hill, London SE5 9RS (tel. 020 3299 3601 or email kch-tr.PALS@nhs.net). **University College London Hospitals NHS Foundation Trust PALS**, 250 Euston Road, London, NW1 2PG (tel: 0203 4567890 email: pals@uclh.nhs.uk). **Queen Mary's PALS,** Frognal Pl, Sidcup, Kent DA14 6LT (Tel: 0208 3085449 email: slh-tr.qm-pals@nhs.net) **Bromley Hospitals PALS,** Princess Royal University Site, Farnborough Common, Orpington, Kent BR6 8ND (Tel: 0168 9863252 email: slh-tr.br-pals@nhs.net) **Queen Elizabeth PALS,** Stadium Road, Woolwich, London SE18 4QH **(**tel: 0208 8364592 email: pals.geht@nhs.net). **St George's Healthcare PALS**, St George's Healthcare NHS Trust, Blackshaw Road, Tooting, London, SW17 0QT (tel: 0208 7252453). **Cumbria Partnership NHS Foundation Trust Patient Experience Team**, Carleton Clinic, Cumwhinton Drive, Carlisle, Cumbria CA1 3SX (tel: 0800 633 5547 email: PET@cumbria.nhs.uk. **Plymouth Hospitals PALS**, Patient Advice & Liaison Service, Patient Services Office, Level 7 Derriford Hospital, Plymouth PL6 8DH (tel: 08451558123 email: plh-tr.PALS@nhs.net). **Adelaide Health Centre (Patient Experience Service)**, Western Community Hospital, William Macleod Way, Southampton, Hampshire, SO16 4XE (tel: 0800 013 2319 email: soc-pct.schpatientexperience@nhs.uk).

Will my taking part in the study be kept confidential?
Yes. All information about your participation in this study will be kept confidential in accordance with the Data Protection Act 1998. Once the survey is complete, your name on the consent form will be kept separately from the survey data, and a linking participant ID number will be used, making it anonymised. Your information will be stored on secure computers, locked within offices and in locked file cabinets, and will only be available to members of the research team. This information will only be used for the purposes of the current study. Your study data will be retained for a minimum of 5-years and subsequently disposed of securely. Your responses to our questions will remain completely

confidential unless you tell us something to indicate that your own health and safety are currently in danger. Your anonymised data will be shared with other researchers and may be used for other research purposes. Please note, the deadline to request withdrawal of your data from the study will be October 2014.

What will happen if I don't want to carry on with the study?
You are free to withdraw from the study at any time without having to give a reason even if you decide to take part initially.

What will happen to the results of the research study?
The results will be used to help the researchers better understand MS pain with a view to developing future treatments. The study will be presented at scientific conferences and be written up for publication in scientific journals. We will provide you with a summary sheet of the results.

Who is organizing and funding the research?
The study is funded by the Multiple Sclerosis Society. It is being organized and conducted by researchers from The Health Psychology Department, Institute of Psychiatry, King's College London.

Who has reviewed the study?
The study has been reviewed by the (Queen's Square) NHS Research Ethics Committee (REC) (13/LO/1429), and by the research development team and patient and public involvement members at the UK Multiple Sclerosis Society.

What if I have questions about the project? Contact details for further information
If you would like to discuss your potential involvement in this research further please contact:

Name: Mr Anthony Harrison
Job title: Principal Investigator (Doctoral Student)
Telephone number: 07936 448 926 Email address: anthony.harrison@kcl.ac.uk

Address: Department of Health Psychology, Institute of Psychiatry, Kings College

London, 5th Floor Bermondsey Wing, Guys Campus, London SE1 9RT

ALTERNATIVELY: Fill in the attached contact details form, return it in a stamped

addressed envelope and one of the researchers will contact you

Please retain this information sheet.

If, after discussing the research with us, you decide that you wish to participate we will ask you to complete and return a consent form. You will get a copy of the consent form to keep.

Appendix K. Chapter 5 Cross-sectional study: Consent Form

Participant Identification Number:

KING'S College LONDON
University of London

CONSENT FORM

Pain Experience in MS (PEMS) Study (Study ethics Ref: 13/LO/1429)

Please complete this form if you think you might be interested in taking part in this study.

Please initial at the end of each statement to confirm

1. I confirm that I have read and understand the information sheet (dated 14th August 2013, version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily **……**

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected **…….**

3. I consent to the processing of my data in accordance with the Data Protection Act (1998) **……**

4. I agree to take part in the above study **……**

5. I give permission for my unidentifiable data to be used for future research **……**

6. I agree to a researcher from the Health Psychology Department, King's College London contacting me to discuss my potential involvement in this research project **……**

7. I understand that by giving my name and contact details I am not obliged to take part. **……**

8. I agree to be contacted by the researcher to be informed about future studies **……**

Please select either: 'Yes' to opt-in ☐ Or 'No' to opt-out ☐

Name of Participant_____ **Date**_____**Signature**_____

Telephone number/s: ……..

Best days/times to contact me ……

Email address (if checked regularly):…….

When completed: 1 copy for the patient; 1 for researcher's file.

Appendix L. Chapter 5 Cross-sectional Study: Demographic and Disease Questionnaire

Questions about you

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. Your date of birth (DD/MM/YY): ...../...../.....

3. What is your gender: ☐ Male ☐ Female

4. What is your ethnicity?

☐ White - English / Welsh / Scottish / Northern Irish / British	☐ Mixed / Multiple ethnic group - White and Black Caribbean	☐ Asian / Asian British – Indian	☐ Black / African / Caribbean / Black British – African
☐White - Irish	☐ Mixed / Multiple ethnic group - White and Black African	☐ Asian / Asian British – Pakistani	☐ Black / African / Caribbean / Black British – Caribbean
☐White - Gypsy or Irish Traveller	☐ Mixed / Multiple ethnic group - White and Asian	☐ Asian / Asian British – Bangladeshi	☐ Black / African / Caribbean / Black British – Any other Black / African / Caribbean background
☐White - Any Other White background	☐ Mixed / Multiple ethnic group - Any Other Mixed / multiple ethnic background	☐ Asian / Asian British – Chinese ☐ Asian / Asian British - Any other Asian background	☐ Other ethnic group – Arab ☐ Other ethnic group – Any other ethnic group ☐ Not known/not provided

5. Present relationship status: ☐ Single ☐ Married ☐ Widowed ☐ Separated/divorced ☐ Co-habiting

6. How many years of education have you completed? …… *Years*

7. Which of the following best describes your current job status?

☐ Employed outside the home, full-time ☐ Employed outside the home, part-time

☐ Homemaker ☐ Retired ☐ Unemployed ☐ Other

<u>If unemployed</u>, are you not working due to your MS? ☐ Yes ☐ No

Questions about your MS & Other Conditions

Are you currently experiencing a relapse? ☐ Yes ☐ No ☐ Not applicable

8. When was your MS diagnosed? (DD/MM/YY): ...../...../.....

9. The next question asks you about whether you experience certain MS symptoms, and then

asks how much this symptom interferes with your life?

(Tick 'Yes' or 'No' if you experience this symptom and then rate how much it interferes.)

Pain					Yes ☐				No ☐	
0 Does Not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

Fatigue					Yes ☐				No ☐	
0 Does Not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

Problems with bowel or bladder					Yes ☐				No ☐	
0 Does Not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

Balance Difficulties					Yes ☐				No ☐	
0 Does Not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

Problems with memory or thinking					Yes ☐				No ☐	
0 Does Not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

Blurred or double vision					Yes ☐				No ☐	
0 Does Not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

Difficulties with Speech					Yes ☐				No ☐	
0 Does Not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

Difficulties with swallowing					Yes ☐				No ☐	
0 Does Not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

Stiffness and spasms in muscles Yes ☐ No ☐										
0 Does Not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

Sexual Problems Yes ☐ No ☐										
0 Does Not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

Tremor Yes ☐ No ☐										
0 Does Not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

Other……(please state)										
0 Does Not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

10. Have you ever been diagnosed with any other physical or psychiatric condition (e.g. depression, anxiety, schizophrenia) other than MS? ☐ Yes ☐ No

If 'yes', what condition/s?_____

I heard about this study through the

NHS neurology / MS specialist service: ☐ Yes ☐ No

If 'no', I heard about this study through the *(please tick):*

MS Society UK ☐

Local MS Therapy Centre ☐

SHIFT Website ☐

MS Register UK ☐

NHS ☐

Other (*please state*)

_____

If through the NHS, can you tell us which Trust /hospital:

King's College Hospital ☐

Guy's & St. Thomas' ☐

Cumbria ☐

South London Healthcare ☐

Queen Elizabeth Hospital, Woolwich ☐

University College London Institute of Neurology, NMR Research Unit ☐

Wolfson Research Unit, University College London ☐

University College London Outpatient Clinic ☐

St. George's Hospital, Tooting ☐

Cumbria Hospitals NHS Foundation Trust ☐

Turner Centre, St James Hospital, Portsmouth ☐

Plymouth Hospitals NHS Trust ☐

Royal Devon & Exeter Hospitals NHS Trust ☐

Sussex Community NHS Trust

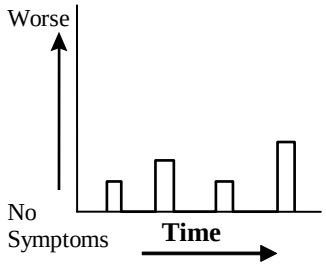
Derby Hospitals ☐

Ashford & St Peter's Hospitals NHS Trust ☐

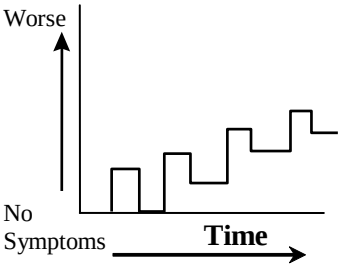
Harrogate and District NHS Foundation Trust ☐

Southampton Solent Healthcare ☐

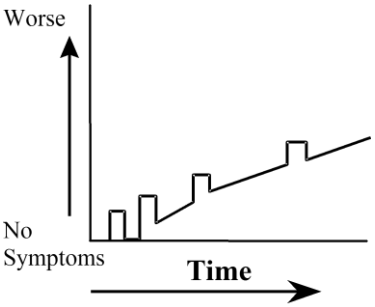
Self-administered Multiple sclerosis Disease Course Questionnaire
(Bamer et al., 2007)
Check *only* one box that best describes your *MS disease activity over time*



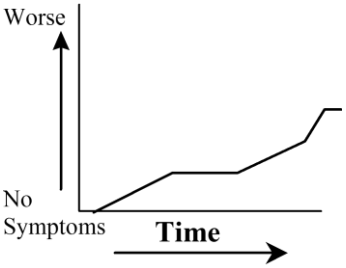
☐ Attacks (exacerbations, relapses) come on over a few hours or days, last from one day to several weeks, but once they are over, you feel the same as you always have.



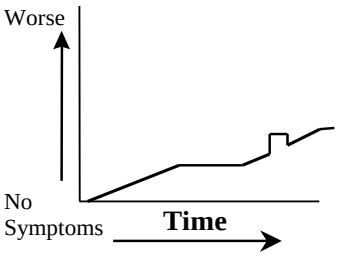
☐ Attacks (exacerbations, relapses) come on over a few hours or days, last from one day to several weeks. After some attacks, your symptoms are worse than before. The symptoms that remain after the attack are stable until a new attack occurs.



☐ At the start of the disease, attacks (exacerbations, relapses) occur. You may feel your symptoms get worse because of these attacks. Then even between the attacks, you feel you are getting worse. In some cases, attacks cease, yet your symptoms continued to worsen.



☐ Symptoms worsen from the beginning. Your symptoms may be stable for a time, gradually worsen, or deteriorate rapidly, but attacks (exacerbations, relapses) have never occurred.



☐ Symptoms gradually worsen from the beginning. Your symptoms may be stable for a time at the beginning, or may deteriorate rapidly. Attacks (exacerbations, relapses) did not occur at the start, but may occur later in the course of the disease.

Self-report EDSS (EDSS-S) Mobility Scale (Bowen et al., 2001)

WALKING DISTANCES

We would like to know how well your body functions on an average day, not your worst days and not your best days. Please tick the box that most closely matches your abilities.**

On an average day I can:

☐ Walk more than 500 metres (about 530 yards) without stopping to rest.
(This is approximately 5 football field lengths.)
I would need ☐ no help ☐ a cane ☐ two canes ☐ a walker

☐ Walk 300 metres (about 350 yards) without stopping to rest.
(This is approximately 3 football field lengths.)
I would need ☐ no help ☐ a cane ☐ two canes ☐ a walker

☐ Walk 200 metres (about 200 yards) without stopping to rest.
(This is approximately 2 football field lengths.)
I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

☐ Walk 100 metres (about 100 yards) without stopping to rest.
(This is approximately 1 football field length.)
I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

☐ Walk 20 metres (about 60 feet) without stopping to rest.
I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

☐ Walk 5 metres (about 15 feet) without stopping to rest
I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

☐ Walk a few steps.
I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

☐ Use a wheelchair

If you use a wheelchair please **tick one** of the following 4 statements:

1. ☐ On an average day, I can bear my weight with my legs (stand up and move) and get myself from one chair to another.
2. ☐ On an average day, I can bear my weight (with the strength in my arms) and lift myself from one chair to another.
3. ☐ On an average day, I cannot bear any weight or get myself from one chair to another.
4. ☐ On an average day, I cannot sit up in a chair.

Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994)

About the Pain You Experience

1. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.										
0 No Pain	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Pain as bad as you can imagine**
2. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.										
0 No Pain	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Pain as bad as you can imagine**
3. Please rate your pain by circling the one number that best describes your pain on the average.										
0 No Pain	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Pain as bad as you can imagine**
4. Please rate your pain by circling the one number that tells how much pain you have right now.										
0 No Pain	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Pain as bad as you can imagine**
6. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.										
0 No Relief	**10%**	**20%**	**30%**	**40%**	**50%**	**60%**	**70%**	**80%**	**90%**	**100% Complete Relief**

7. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 Does Not Interfere	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Completely Interferes**

B. Mood

0 Does Not Interfere	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Completely Interferes**

C. Mobility (Getting around)

0 Does Not Interfere	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Completely Interferes**

D. Normal Work (includes both work outside the home and housework)

0 Does Not Interfere	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Completely Interferes**

E. Relations with other people

0 Does Not Interfere	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Completely Interferes**

F. Sleep

0 Does Not Interfere	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Completely Interferes**

G. Enjoyment of Life

0 Does Not Interfere	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Completely Interferes**

8. Where is your pain located? Please indicate if more than one location.					
Head ☐	Face ☐	Eyes ☐	Ears ☐	Mouth ☐	Nose ☐
Chest/ upper torso ☐	Stomach/ Lower torso ☐	Viscera/sides ☐			
Shoulders ☐	Arms ☐	Forearms ☐	Hands ☐	Fingers ☐	
Upper-back ☐	Mid-back ☐	Lower-back ☐	Backside ☐	Hips ☐	Groin ☐
Thighs ☐	Knees ☐	Calves ☐	Shins ☐	Feet ☐	

9. When did you begin experiencing pain related to your MS? *……Years …… Months ago*

10. Does your pain come and go? ☐ Yes ☐ No

… **Or is it always present?** ☐ Yes ☐ No

If you pain comes and goes, can you estimate how many days per month do you have pain _____

11. What treatments or medications are you receiving for your pain?					
			Number per day?	**Used regularly**	**…or as required**
Paracetamol ☐				Yes ☐ No ☐	Yes ☐ No ☐
Ibuprofen ☐	Diclofenac ☐			Yes ☐ No ☐	Yes ☐ No ☐
Codeine ☐	Co-codamol ☐	Tramadol ☐		Yes ☐ No ☐	Yes ☐ No ☐
Morphine ☐	Bupranorphine ☐	Oxycontin ☐		Yes ☐ No ☐	Yes ☐ No ☐
Amitriptyline ☐	Duloxetine ☐			Yes ☐ No ☐	Yes ☐ No ☐
Gabapentin ☐	Pregabilin ☐	Carbamazepine ☐		Yes ☐ No ☐	Yes ☐ No ☐
Lignocaine patch ☐				Yes ☐ No ☐	Yes ☐ No ☐
Smoked cannabis ☐	Sativex spray ☐			Yes ☐ No ☐	Yes ☐ No ☐
Other: _____ _____				Yes ☐ No ☐	Yes ☐ No ☐

Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983)

Researchers and clinicians are aware that emotions play an important role in most illness. This questionnaire is designed to help the researcher to know how you feel. Read each item and place a firm tick in the box opposite the reply which comes to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

Tick <u>only one grey box</u> for each section:

1. I feel tense or wound up:		**6. I feel cheerful:**	
Most of the time…….		*Not at all……*	
A lot of the time…….		*Not often……*	
Time to time, occasionally.		*Sometimes……*	
Not at all……		*Most of the time……*	

2. I still enjoy the things I used to:		**7. I can sit at ease and feel relaxed:**	
Definitely as much……...		*Definitely……*	
Not quite so much……		*Usually……*	
Only a little……...		*Not often……*	
Hardly at all……...		*Not at all……..*	

3. I get a sort of frightened feeling as if something awful is about to happen:		**8. I feel as if I am slowed down:**	
Very definitely & quite badly		Nearly all the time……	
Yes, but not too badly		Very often……	
A little, but it doesn't worry me		Sometimes……	
Not at all……		Not at all……	

4. I can laugh and see the funny side of things:		**9. I get a sort of frightened feeling like 'butterflies' in the stomach:**	
As much as I always could……..		Not at all…….....	
Not quite as much now……		Occasionally……	
Definitely not so much now……..		Quite often……	
Not at all……..		Very often……..	

5. Worrying thoughts go through my mind:		**10. I have lost interest in my appearance;**	
A great deal of the time……...		*Definitely……*	
A lot of the time……		*I don't take as much care as I should……..*	
From time to time but not too often.		*I may not take quite as much care as ever……..*	
Only occasionally ……		*I take just as much care as ever……*	

11. I feel restless as if I have to be on the move:		**13. I get sudden feelings of panic:**	
Very much indeed……...		*Very often indeed……*	
Quite a lot……		*Quite often……*	
Not very much……...		*Not very often……*	
Not at all……		*Not at all……*	

12. I look forward with enjoyment to things:		**14. I can enjoy a good book or radio or TV programme:**	
As much as ever did……..		*Often……...*	
Rather less than I used to……...		*Sometimes……*	
Definitely less than I used to……		*Not often……..*	
Hardly at all……		*Very seldom……*	

Kiel Pain Inventory Avoidance-Endurance Measure
Pain-related Behavioural Responses (KPI-AEM-PBR) (Hasenbring et al., 2009)

A number of actions are set out below which we may observe in ourselves when we are in pain. How we behave is often dependent on the severity of this pain at any given moment. Please go through **each of the following statements** and check both scales to indicate if and how often you have acted in such a way **in the past 14 days** when you experienced **mild** and/or **severe pain**.

Please select one of the numbers on each scale:

		I behave this way when I have mild pain...							I behave this way when I have severe pain...						
	When I am in pain.....	never	almost never	seldom	sometimes	often	mostly	always	never	almost never	seldom	sometimes	often	mostly	always
1	... I stop doing physically demanding activities.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
2	… I avoid visiting my friends.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
3	... I take a rest.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
4	…I take care not to let myself go.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
5	... I try not to take any notice of it	0	1	2	3	4	5	6	0	1	2	3	4	5	6
6	... I clench my teeth.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
7	... I cancel private appointments.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
8	... I cancel a visit to an event.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
9	…I avoid physically strenuous activities.	0	1	2	3	4	5	6	0	1	2	3	4	5	6

	When I am in pain.....	I behave this way when I have mild pain… never	almost never	seldom	sometimes	often	mostly	always	I behave this way when I have severe pain... never	almost never	seldom	sometimes	often	mostly	always
10	... I avoid doing sports.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
11	... I say to myself: "Don`t make such a fuss!".	0	1	2	3	4	5	6	0	1	2	3	4	5	6
12	...I keep my appointments even though I don`t feel up to it.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
13	... I laugh heartily anyway.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
14	... I break off a meeting with friends.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
15	... I tell myself: "I don't have time for this right now!"	0	1	2	3	4	5	6	0	1	2	3	4	5	6
16	... I take it with a laugh.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
17	... I let my family persuade me into things, even I don't feel like it.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
18	... I call my guests to cancel an invitation.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
19	... I carry on doing what I am doing no matter what.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
20	... I hand over strenuous activities.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
21	... I avoid other people's company.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
22	... I distract myself with physical activity.	0	1	2	3	4	5	6	0	1	2	3	4	5	6
23	... I distract myself by doing little jobs at home	0	1	2	3	4	5	6	0	1	2	3	4	5	6

Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995)

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

When I'm in pain… (*Please tick one grey box for each statement.)*

1. I worry all the time about whether the pain will end.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

2. I feel I can't go on.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

3. It's terrible and I think it's never going to get any better.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

4. It's awful and I feel that it overwhelms me.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

5. I feel I can't stand it anymore.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

6. I become afraid that the pain will get worse.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

7. I keep thinking of other painful events.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

8. I anxiously want the pain to go away.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

9. I can't seem to keep it out of my mind.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

10. I keep thinking about how much it hurts.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

11. I keep thinking about how badly I want the pain to stop.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

12. There's nothing I can do to reduce the intensity of the pain.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

13. I wonder whether something serious may happen.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

Chronic Pain Acceptance Questionnaire-8 items (CPAQ-8)
(Fish et al., 2010)

Below you will find a list of statements. Please rate the truth of each statement as it applies to you by circling a number.

Use the following rating scale to make your choices (*Please tick one grey box for each statement.)*

1. I am getting on with the business of living no matter what my level of pain is.

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

2. Keeping my pain level under control takes first priority whenever I'm doing something.

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

3. Although things have changed, I am living a normal life despite my chronic pain.

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

4. Before I can make any serious plans, I have to get some control over my pain.

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

5. I lead a full life even though I have chronic pain.

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

6. When my pain increases, I can still take care of my responsibilities.

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

7. I avoid putting myself in situations where my pain might increase.

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

8. My worries and fears about what pain will do to me are true

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

Illness Perceptions Questionnaire Revised (IPQ-R) (Moss-Morris et al., 2002)

	VIEWS ABOUT YOUR MS-RELATED PAIN	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
IP1*	My MSP will last a short time					
IP2	My MSP is likely to be permanent rather than temporary					
IP3	My MSP will last for a long time					
IP4*	This MSP will pass quickly					
IP5*	I expect to have this MSP for the rest of my life					
IP6	My MSP is a serious condition					
IP7	My MSP has major consequences on my life					
IP8*	MY MSP does not have much of an effect on my life					
IP9	My MSP strongly affects the way others see me					
IP10	My MSP has serious financial consequences					
IP11	My MSP causes difficulties for those who are close to me					
IP12	There is a lot which I can do to control my MSP					
IP13	What I do can determine whether my MSP gets better or worse					
IP14	The course of my MSP depends on me					

VIEWS ABOUT YOUR MS-RELATED PAIN		STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
IP15 *	Nothing I do will affect my MSP					
IP16	I have the power to influence my MSP					
IP17 *	My actions will have no effect on the outcome of my MSP					
IP18 *	My MSP will improve in time					
IP24	The MSP of my condition are puzzling to me					
IP25	My MSP is a mystery to me					
IP26	I don't understand my MSP					
IP27	My MSP doesn't make any sense to me					
IP28 *	I have a clear picture or understanding of my MSP					
IP29	The symptoms of my MSP change a great deal from day to day					
IP30	My MSP come and go in cycles					
IP31	My MSP is very unpredictable					
IP32	I go through cycles in which my MSP gets better and worse.					
IP33	I get depressed when I think about my MSP					
IP34	When I think about my MSP I get upset					
IP35	My MSP makes me feel angry					

VIEWS ABOUT YOUR MS-RELATED PAIN		STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
IP36	My MSP does not worry me					
IP37	Having this MSP makes me feel anxious					
IP38	My MSP makes me feel afraid					

Cognitive Fusion Questionnaire (CFQ) (Gillanders et al., 2014)

Below you will find a list of statements. Please rate how true each statement is for you by ticking one grey box for each statement.

1. My thoughts cause me stress & emotional pain

Never True	Very Seldom true	Seldom True	Sometimes True	Frequently True	Almost Always True	Always True

2. I get so caught up in my thoughts that I am unable to do the things that I most want to do

Never True	Very Seldom true	Seldom True	Sometimes True	Frequently True	Almost Always True	Always True

3. I over-analyze situations to the point where it's unhelpful to me

Never True	Very Seldom true	Seldom True	Sometimes True	Frequently True	Almost Always True	Always True

4. I struggle with my thoughts

Never True	Very Seldom true	Seldom True	Sometimes True	Frequently True	Almost Always True	Always True

5. I get upset with myself for having certain thoughts

Never True	Very Seldom true	Seldom True	Sometimes True	Frequently True	Almost Always True	Always True

6. I tend to get very entangled in my thoughts

Never True	Very Seldom true	Seldom True	Sometimes True	Frequently True	Almost Always True	Always True

7. It is such a struggle to let go of upsetting thoughts even when I know that letting go would be helpful

Never True	Very Seldom true	Seldom True	Sometimes True	Frequently True	Almost Always True	Always True

Thank you for completing this questionnaire

In order to send you a **debriefing statement, summary of findings** and a **£5 Marks & Spencer gift voucher** for completing the questionnaire, please tell us your name and postal address (*optional*):

Name:_____

Address: _____

_____ Postcode: _____

Appendix N. Chapter 7 Case Series: Post-treatment telephone interview schedule

Questions	Prompts
1. First of all can you start by telling me what you were expecting from the eight sessions?	-What did you think the programme would be like? -In what ways (if any) did you think it might help you?
2. How did you find the programme overall?	-Tell me how you found your first session -Tell me about the other sessions -Tell me how you found using the treatment booklet and task sheets -Tell me how you found the homework tasks - What about the telephone/skype support sessions? How did you find them? - Do you have any other thoughts about different or additional support alongside the programme?
3. Can you tell me what you liked about the programme?	-What was helpful? Why? How? -Were there some sessions/ some aspects that were more helpful than others?
4. Can you tell me what you disliked about the programme?	-What was unhelpful? Why? How? -Were there some sessions/ some aspects that were less helpful than others?
5. Tell me about anything that you feel has changed from having done the programme?	-Can you tell me what changed? (Anything different in your day-to-day life, the way you are dealing with MS pain?) -Can you tell me how you came to notice things changing? -Why/how do you think things changed?
6. What do you think of the questionnaires used and the overall set up of the study?	-Any further comments regarding the questionnaires used?
7. Do you have anything else you would like to tell me about your experiences of this programme that haven't already covered?	-What would you feed back to the people who put together the programme? -What advice would you give to people thinking about taking part in CBT-based programmes? - If I were to take one key message away with me today as a researcher about your experience of the programme what would it be?

Appendix O. Case Series: Participant's pain medication use at pre-treatment and pain relief

ID	Reported Pain Medications	Pre-treatment Pain Relief from Medications % (BPI)[2]
1	Paracetamol (as required) Ibuprofen (as required) Codiene (as required) Co-codamol (as required) Duloxetine (60mgs daily) Pregabilin (600mg daily) Tegretol (200mg x 2 daily) Lamotrigine (100mg daily) Smoked cannabis (very infrequently)	10
2	Ibuprofen once or twice a week (800mg to 2400mg daily) Sativex (single bottle weekly)	75
3	Amitriptyline (20mg Daily) Pregabilin (300mg Daily)	60
4	Co-codamol (500mg as required) Baclofen (20mg to 30mg daily) Gabapentin (900mg daily)	50
5	Ibuprofen (200mg daily) Co- codamol (from 30mg to 500mg daily)	90
6	Gabapentin (2100mg daily). Clonazepam (750mg daily). Paracetamol (500mg to 1000mg daily as required).	30
7	Sativex (6 sprays daily) Gabapentin (1200mg daily) Amitriptyline (50mg daily) Baclofen (40mg daily).	90

ID: Participant identification number; [2]BPI: Brief Pain Inventory Short Form on entering the study.

Appendix P. Chapter 7 Case Series: Simulation Modelling Analysis (SMA) output primary outcomes

P.1 Treatment and maintenance effects for Pain Severity 4 day ratings (BPI) tested using SMA

	Baseline (Phase A) versus Treatment (Phase B)					Baseline (Phase A) versus Follow-up (Phase C)				
ID	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[1]**	**Slope *r* (*P*)[1]**	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[2]**	**Slope *r* (*P*)[2]**
	A	**B**				**A**	**C**			
1	6.63	4.50	0.36	1.42 (.029*)+	0.50 (.078)	6.63	3.88	0.01	1.64 (.007**)+	-0.60 (.020*)
2	3.75	3.25	0.24	0.65 (.240)	-0.15 (.580)	3.75	3.0	0.37	0.90 (.292)	-0.52 (.151)
3	6.63	6.56	0.44	0.04 (.952)	0.26 (.436)	6.63	6.88	0.28	0.22 (.767)	.19 (.579)
4	6.00	3.68	0.16	0.93 (.083)	-0.54 (.017**)	6.00	3.5	-0.03	0.93 (.100)	-.13 (.619)
5	3.50	4.19	0.19	0.30 (.555)	0.21 (.414)	3.50	5.62	0.39	1.01 (.228)	0.61 (.076)
6	3.75	6.25	0.70	1.67 (.087)	0.81 (.018**)	3.75	7.25	0.81	3.40 (.023*)	0.866 (.031*)
7	7.12	5.75	0.51	1.15 (.128)	-0.66 (.030*)	7.12	5.25	0.47	1.66 (.080)	-0.74 (.023*)

SMA: Simulation Modelling Analysis; BPI = Brief Pain Inventory short-form; ID: Participant identification number**;** *M:* Phase mean values; *AR*: Pooled phases autocorrelation estimate *(r* Lag (1)); *P*: p-value accounting for autocorrelation; *r*: Pearson's *r* correlation.

[1]10000 null distribution simulations generated; Error of mean = 0; Standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 24: Phase A (baseline) = 8; Phase B (treatment) = 16. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's *d*; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during treatment (0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16).

[2]10000 null simulations generated; Error of mean =0; standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 16: Phase B (baseline) = 8; Phase C (follow-up) = 8. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's *d*; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during follow-up (0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8).

** = Effect size significant at the 0.01 level

* = Effect size significant at the 0.05 level

+ = Significant at the 0.05 level after manually imputing *AR*=.40.

d = 0.2 = small, 0.5 = medium = 0.8 = large effect size; *r*= 0.1 = small, 0.3 = medium and 0 .5 = large effect size.

P.2 Treatment and maintenance effects for Pain Interference 4 day ratings (BPI) tested using SMA

	Baseline (Phase A) versus Treatment (Phase B)					Baseline (Phase A) versus Follow-up (Phase C)				
ID	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[1]**	**Slope *r* (*P*)[1]**	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[2]**	**Slope *r* (*P*)[2]**
	A	**B**				**A**	**C**			
1	6.63	3.38	0.40	1.50 (.030*)	-0.33 (.289)	6.63	3.50	-0.05	1.42 (.013**)	-0.51 (.037*)
2	4.00	3.25	0.28	1.04 (.076)	-0.26 (.356)	4.00	2.88	0.56	1.35 (.193)	-0.70 (.076)
3	6.75	6.44	0.36	0.22 (.722)	0.19 (.542)	6.75	6.75	0.31	0.00 (1.000)	0.15 (.6765)
4	5.38	1.81	0.64	1.50 (.100)	-0.77 (.019*)	5.37	1.12	0.25	2.58 (.002**)+	-0.61 (.046*)
5	2.50	3.94	0.24	0.61 (.275)	0.34 (.191)	2.50	5.34	0.47	1.28 (.164)	0.65 (.066)
6	7.75	8.50	0.45	0.58 (.383)	.59 (.052*)	7.75	9.25	0.42	1.25 (.1643)	0.622 (.083)
7	8.12	5.81	0.41	1.44 (.044*)	-0.68 (.009**)	8.12	5.12	0.38	1.90 (.029*)+	-0.72 (.020*)+

SMA: Simulation Modelling Analysis; BPI = Brief Pain Inventory short-form; ID: Participant identification number**;** *M:* Phase mean values; *AR*: Pooled phases autocorrelation estimate *(r* Lag (1)); *P*: p-value accounting for autocorrelation; *r*: Pearson's *r* correlation.

[1]10000 null distribution simulations generated; Error of mean = 0; Standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 24: Phase A (baseline) = 8; Phase B (treatment) = 16. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's *d*; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during treatment (0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16).

[2]10000 null simulations generated; Error of mean =0; standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 16: Phase B (baseline) = 8; Phase C (follow-up) = 8. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's *d*; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during follow-up (0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8).

** = Effect size significant at the 0.01 level

* = Effect size significant at the 0.05 level

+ = Significant at the 0.05 level after manually imputing *AR*=.40.

d = 0.2 = small, 0.5 = medium = 0.8 = large effect size; *r*= 0.1 = small, 0.3 = medium and 0 .5 = large effect size.

Appendix Q. Chapter 7 case series: Simulation Modelling Analysis (SMA) output secondary process variables

Q.1 Treatment and maintenance effects for Pain Catastrophizing 4 day ratings (PCS) tested using SMA

	Baseline (Phase A) versus Treatment (Phase B)					Baseline (Phase A) versus Follow-up (Phase C)				
ID	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[1]**	**Slope *r* (*P*)[1]**	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[2]**	**Slope *r* (*P*)[2]**
	A	**B**				**A**	**C**			
1	30.38	16.28	0.58	1.76 (.036*)	-0.63 (.074)	30.38	9.00	0.56	2.58 (.015**)	-0.68 (.078)
2	30.25	13.81	0.77	3.90 (.001**)	-0.69 (.121)	30.25	12.00	0.75	4.39 (.002**)	-0.80 (.064)
3	30.63	27.17	-0.30	0.72 (.033*)	-0.235 (.131)	30.62	26.11	0.06	1.25 (.034*)	-0.44 (.088)
4	34.38	19.13	0.84	1.96 (.098)	-0.92 (.001**)	34.37	5.00	0.85	9.85 (<.001**)	-0.86 (.042*)
5	40.75	39.25	0.19	0.37 (.483)	-0.09 (.701)	40.75	43.65	0.58	0.77 (.465)	0.51 (.270)
6	42.37	42.50	0.45	0.04 (.953)	0.36 (.287)	42.37	43.65	0.45	0.45 (.609)	0.43 (.281)
7	34.0	32.06	0.68	0.41 (.659)	-0.67 (.089)	34.0	28.0	0.66	1.35 (.249)	-0.86 (.010**)

SMA: Simulation Modelling Analysis; PCS*:* Pain Catastrophizing Scale; ID: Participant identification number**;** *M:* Phase mean values; *AR*: Pooled phases autocorrelation estimate *(r* Lag (1)); *P*: p-value accounting for autocorrelation; *r*: Pearson's *r* correlation.

[1]10000 null distribution simulations generated; Error of mean = 0; Standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 24: Phase A (baseline) = 8; Phase B (treatment) = 16. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's *d*; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during treatment (0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16).

[2]10000 null simulations generated; Error of mean =0; standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 16: Phase B (baseline) = 8; Phase C (follow-up) = 8. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's d; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during follow-up (0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8). ** = Effect size significant at the 0.01 level

* = Effect size significant at the 0.05 level

d = 0.2 = small, 0.5 = medium = 0.8 = large effect size; *r*= 0.1 = small, 0.3 = medium and 0 .5 = large effect size.

Q.2 Treatment and maintenance effects for Pain Acceptance 4 day ratings (CPAQ) tested using SMA

	Baseline (Phase A) versus Treatment (Phase B)					Baseline (Phase A) versus Follow-up (Phase C)				
ID	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[1]**	**Slope *r* (*P*)[1]**	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[2]**	**Slope *r* (*P*)[2]**
	A	**B**				**A**	**C**			
1	30.88	32.56	0.37	0.30 (.618)	-0.11 (.725)	30.88	32.67	0.28	0.28 (.680)	0.14 (.670)
2	23.13	24.27	0.36	1.67 (.016**)	0.51 (.070)	23.13	22.00	-0.04	0.22 (.670)	0.45 (.059*)
3	18.89	19.56	-0.18	0.18 (.628)	0.25 (.161)	18.87	22.62	-.04	1.39 (.016*)	0.50 (.043*)
4	31.38	34.75	0.77	0.90 (.402)	0.71 (.110)	31.38	42.75	0.77	6.86 (<.001**)	0.84 (.045*)
5	17.00	14.18	0.43	1.01 (.140)	-0.44 (.151)	17.0	15.75	0.56	0.47 (.641)	0.03 (.936)
6	11.62	8.81	0.50	0.85 (.242)	-0.44 (.208)	11.62	8.62	0.62	1.19 (.283)	-0.526 (.270)
7	11.62	14.56	0.78	0.77 (.487)	0.81 (.706)	11.62	17.25	0.72	1.85 (.154)	0.91 (.004**)

SMA: Simulation Modelling Analysis; CPAQ-8: Chronic Pain Acceptance Questionnaire 8 items; ID: Participant identification number**;** *M:* Phase mean values; *AR*: Pooled phases autocorrelation estimate *(r* Lag (1)); *P*: p-value accounting for autocorrelation; *r*: Pearson's *r* correlation.

[1]10000 null distribution simulations generated; Error of mean = 0; Standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 24: Phase A (baseline) = 8; Phase B (treatment) = 16. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's *d*; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during treatment (0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16).

[2]10000 null simulations generated; Error of mean =0; standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 16: Phase B (baseline) = 8; Phase C (follow-up) = 8. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's d; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during follow-up (0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8).

** = Effect size significant at the 0.01 level

* = Effect size significant at the 0.05 level;

d = 0.2 = small, 0.5 = medium = 0.8 = large effect size; *r*= 0.1 = small, 0.3 = medium and 0 .5 = large effect size.

Q.3 Treatment and maintenance effects for Avoidance of Social Activities 4 day ratings (ASAS) tested using SMA

	Baseline (Phase A) versus Treatment (Phase B)					**Baseline (Phase A) versus Follow-up (Phase C)**				
ID	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[1]**	**Slope *r* (*P*)[1]**	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[2]**	**Slope *r* (*P*)[2]**
	A	**B**				**A**	**C**			
1	1.46	0.90	0.15	0.49 (0.319)	-0.07 (.778)	1.46	0.46	0.06	0.82 (.151)	-0.33 (.212)
2	3.00	3.00	-	-	-	3.00	3.00	-	-	-
3	2.48	2.62	-0.04	0.32 (0.464)	-0.11 (.557)	2.48	3.14	0.50	2.76 (.006**)	0.80 (.008**)
4	4.93	3.41	0.86	1.91 (0.127)	-0.92 (.004**)	4.93	1.06	0.89	6.86 (<.001**)	-0.92 (.016**)
5	5.50	5.90	0.62	1.58 (0.070)	0.30 (.476)	5.50	5.77	0.54	0.98 (.325)	0.55 (.187)
6	5.81	6.0	0.27	0.77 (0.166)	0.26 (.329)	5.81	6.0	0.27	0.68 (.360)	0.263 (.453)
7	4.0	3.21	0.71	1.62 (0.105)	-.092 (<.001**)	4.0	2.83	0.68	4.69 (<.001**)	-0.89 (<.001**)

SMA: Simulation Modelling Analysis; ASAS: Avoidance of social activities due to pain subscale from the Avoidance-Endurance Questionnaire (AEQ); ID: Participant identification number**;** *M:* Phase mean values; *AR*: Pooled phases autocorrelation estimate *(r* Lag (1)); *P*: p-value accounting for autocorrelation; *r*: Pearson's *r* correlation.

[1]10000 null distribution simulations generated; Error of mean = 0; Standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 24: Phase A (baseline) = 8; Phase B (treatment) = 16. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's *d*; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during treatment (0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16).

[2]10000 null simulations generated; Error of mean =0; standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 16: Phase B (baseline) = 8; Phase C (follow-up) = 8. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's d; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during follow-up (0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8).

** = Effect size significant at the 0.01 level

* = Effect size significant at the 0.05 level; *d* = 0.2 = small, 0.5 = medium = 0.8 = large effect size; *r*= 0.1 = small, 0.3 = medium and 0 .5 = large effect size.

Q.4 Treatment and maintenance effects for Emotional Representations 4 day ratings (BIPQ) tested using SMA

	Baseline (Phase A) versus Treatment (Phase B)					Baseline (Phase A) versus Follow-up (Phase C)				
ID	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[1]**	**Slope *r* (*P*)[1]**	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[2]**	**Slope *r* (*P*)[2]**
	A	**B**				**A**	**C**			
1	4.25	1.38	0.25	1.19 (.038*)	-0.38 (.147)	4.25	0.91	0.18	1.54 (.025*)	-0.54 (.055*)
2	4.75	3.25	0.56	2.76 (.001**)	-0.55 (.121)	4.75	2.75	0.73	2.98 (.029*)	-0.87 (.416)
3	7.88	7.56	-0.13	0.43 (.268)	-0.12 (.525)	7.87	7.5	0.10	0.97 (.154)	-0.231 (.431)
4	6.88	4.56	0.35	1.09 (.082)	-0.61 (.022*)	6.87	1.62	0.62	3.90 (.001**)	-0.83 (.017*)
5	5.38	4.19	-0.16	0.63 (.099)	-0.12 (.506)	5.37	4.0	0.13	0.85 (.019)	0.02 (.919)
6	8.5	8.5	0.01	0.00 (1.000)	0.26 (.209)	8.5	9.0	-0.12	0.82 (.108)	0.204 (.407)
7	8.37	6.56	0.48	1.10 (.136)	-0.73 (.008**)	8.37	5.75	0.45	1.67 (.073)	-0.79 (.009**)

SMA: Simulation Modelling Analysis; BIPQ: Brief Illness Perceptions Questionnaire single item adapted for MS pain; ID: Participant identification number**;** *M:* Phase mean values; *AR*: Pooled phases autocorrelation estimate *(r* Lag (1)); *P*: p-value accounting for autocorrelation; *r*: Pearson's *r* correlation.

[1]10000 null distribution simulations generated; Error of mean = 0; Standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 24: Phase A (baseline) = 8; Phase B (treatment) = 16. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's d; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during treatment (0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16).

[2]10000 null simulations generated; Error of mean =0; standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 16: Phase B (baseline) = 8; Phase C (follow-up) = 8. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's *d*; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during follow-up (0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8).

** = Effect size significant at the 0.01 level

* = Effect size significant at the 0.05 level;

d = 0.2 = small, 0.5 = medium = 0.8 = large effect size; *r* = 0.1 = small, 0.3 = medium and 0 .5 = large effect size.

Q.5 Treatment and maintenance effects for Perceived Consequences 4 day ratings (BIPQ) tested using SMA

	Baseline (Phase A) versus Treatment (Phase B)					Baseline (Phase A) versus Follow-up (Phase C)				
ID	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[1]**	**Slope *r* (*P*)[1]**	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[2]**	**Slope *r* (*P*)[2]**
	A	**B**				**A**	**C**			
1	6.88	4.38	0.19	1.22 (.024*)	-0.37 (.134)	6.88	4.63	0.05	1.28 (.806)	-0.52 (.051*)
2	5.25	3.44	0.60	2.27 (.012**)	.33 (.426)	5.25	2.75	0.73	2.76 (.042*)	-0.80 (.058)
3	7.75	7.25	0.01	0.90 (.051*)	-0.17 (.431)	7.75	9.11	0.03	0.35 (.533)	0.48 (.059*)
4	2.25	4.13	0.39	1.09 (.094)	0.06 (.847)	2.25	1.37	-0.09	0.61 (.230)	-0.33 (.171)
5	4.75	4.19	-0.28	0.30 (.362)	-0.03 (.849)	4.75	4.25	-0.16	0.28 (.544)	0.15 (.510)
6	9.12	9.37	0.09	0.32 (.489)	0.38 (.079)	9.12	9.75	0.02	.98 (0.093)	0.48 (0.058)
7	8.5	6.75	0.62	1.33 (.137)	-0.84 (.001**)	8.5	5.62	0.62	2.87 (.018**)	-0.82 (.016**)

SMA: Simulation Modelling Analysis; BIPQ: Brief Illness Perceptions Questionnaire single item adapted for MS pain; ID: Participant identification number**;** *M:* Phase mean values; *AR*: Pooled phases autocorrelation estimate *(r* Lag (1)); *P*: p-value accounting for autocorrelation; *r*: Pearson's *r* correlation.

[1]10000 null distribution simulations generated; Error of mean = 0; Standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 24: Phase A (baseline) = 8; Phase B (treatment) = 16. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's *d*; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during treatment (0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16).

[2]10000 null simulations generated; Error of mean =0; standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 16: Phase B (baseline) = 8; Phase C (follow-up) = 8. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's d; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during follow-up (0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8).

** = Effect size significant at the 0.01 level

* = Effect size significant at the 0.05 level;

d = 0.2 = small, 0.5 = medium = 0.8 = large effect size; *r*= 0.1 = small, 0.3 = medium and 0 .5 = large effect size.

Q.6 Treatment and maintenance effects for Timeline 4 day ratings (BIPQ) tested using SMA										
	Baseline (Phase A) versus Treatment (Phase B)					**Baseline (Phase A) versus Follow-up (Phase C)**				
ID	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[1]**	**Slope *r* (*P*)[1]**	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[2]**	**Slope *r* (*P*)[2]**
	A	**B**				**A**	**C**			
1	8.63	7.81	0.21	0.61 (.261)	-0.47 (.056*)	8.63	5.88	0.31	1.81 (.025*)	-0.57 (.077)
2	6.00	3.69	0.77	2.34 (.031*)	-0.73 (.076)	6.00	3.00	0.80	2.87 (.046*)	-0.76 (.123)
3	8.38	7.75	0.22	1.09 (.050*)	-0.39 (.124)	8.37	7.0	0.01	0.93 (.102)	-0.30 (.269)
4	7.88	3.94	0.92	1.35 (.336)	0.90 (.017**)	7.87	0.37	0.83	9.85 (<.001**)	0.83 (.065)
5	4.50	4.56	-0.13	0.06 (.874)	-0.02 (.914)	4.5	4.87	-0.36	0.41 (.304)	0.20 (298)
6	10.0	10.0	-	-	-	10.0	10.0	-	-	-
7	8.0	6.87	0.80	0.79 (.4714)	-0.79 (.060)	8.0	5.70	0.80	1.85 (.199)	-0.94 (.001**)

SMA: Simulation Modelling Analysis; BIPQ: Brief Illness Perceptions Questionnaire single item adapted for MS pain; ID: Participant identification number**;** *M:* Phase mean values; *AR*: Pooled phases autocorrelation estimate *(r* Lag (1)); *P*: p-value accounting for autocorrelation; *r*: Pearson's *r* correlation.

[1]10000 null distribution simulations generated; Error of mean = 0; Standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 24: Phase A (baseline) = 8; Phase B (treatment) = 16. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's *d*; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during treatment (0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16).

[2]10000 null simulations generated; Error of mean =0; standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 16: Phase B (baseline) = 8; Phase C (follow-up) = 8. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's d; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during follow-up (0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8).

** = Effect size significant at the 0.01 level

* = Effect size significant at the 0.05 level

d = 0.2 = small, 0.5 = medium = 0.8 = large effect size; *r*= 0.1 = small, 0.3 = medium and 0 .5 = large effect size.

Q.7 Treatment and maintenance effects for Perceived Control 4 day ratings (BIPQ) tested using SMA

	Baseline (Phase A) versus Treatment (Phase B)					Baseline (Phase A) versus Follow-up (Phase C)				
ID	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[1]**	**Slope *r* (*P*)[1]**	**Phase *M***		***AR***	**Level Cohen's *d* (*P*)[2]**	**Slope *r* (*P*)[2]**
	A	**B**				**A**	**C**			
1	6.38	6.75	0.03	0.22 (.616)	0.08 (.709)	6.38	6.88	0.09	0.26 (.655)	0.06 (.839)
2	4.63	3.88	0.19	1.01 (.062)	-0.35 (.155)	4.63	4.38	0.29	0.28 (.694)	-0.13 (.714)
3	5.75	7.06	-0.24	0.58 (.101)	0.29 (.089)	5.75	5.37	-0.30	0.14 (.690)	-.10 (.590)
4	6.38	4.19	0.58	0.75 (.355)	0.193 (.649)	6.37	6.5	-0.14	0.06 (.863)	0.07 (.770)
5	3.00	3.81	-0.10	0.68 (.092)	0.10 (.602)	3.0	3.87	0.19	1.15 (.088)	0.35 (.252)
6	2.87	2.75	-0.14	0.17 (.675)	-0.05 (.784)	2.87	2.62	-0.15	0.31 (0.524)	0.02 (0.901)
7	5.87	5.68	0.19	0.14 (.790)	-0.40 (.100)	5.87	4.75	-.073	0.90 (.092)	-0.43 (.074)

SMA: Simulation Modelling Analysis; BIPQ: Brief Illness Perceptions Questionnaire single item adapted for MS pain; ID: Participant identification number**;** *M:* Phase mean values; *AR*: Pooled phases autocorrelation estimate *(r* Lag (1)); *P*: p-value accounting for autocorrelation; *r*: Pearson's *r* correlation.

[1]10000 null distribution simulations generated; Error of mean = 0; Standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 24: Phase A (baseline) = 8; Phase B (treatment) = 16. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's *d*; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during treatment (0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16).

[2]10000 null simulations generated; Error of mean =0; standard deviation = 1; Valid phase *n*-size of sample (for each individual) = 16: Phase B (baseline) = 8; Phase C (follow-up) = 8. Level change vector (0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1) converted to Cohen's d; SMA's predefined 'Slope vector 2' with a stable baseline and gradual change during follow-up (0, 0, 0, 0, 0, 0, 0, 0, 1, 2, 3, 4, 5, 6, 7, 8).

** = Effect size significant at the 0.01 level

* = Effect size significant at the 0.05 level

d = 0.2 = small, 0.5 = medium = 0.8 = large effect size; *r*= 0.1 = small, 0.3 = medium and 0 .5 = large effect size

Appendix R. Chapter 6 Case Series: Participant Information Sheet

KING'S College LONDON

University of London

Guy's and St Thomas' NHS

NHS Foundation Trust

INFORMATION SHEET FOR PARTICIPANTS

REC Reference Number: 14/LO/1909

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

Study title: Guided cognitive behavioural selF-help Treatment for multiple sclerosis pain (GIFT Study)

We would like to invite you to participate in this original research project. You should only participate if you want to. Choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information (contact details on page 5).

- **Part 1** tells you the purpose of this study and what will happen to you if you take part.
- **Part 2** gives you more detailed information about the conduct of the study.

Who is conducting the study?
This study is part of a larger research project that is being conducted by researchers at The Section of Health Psychology, Institute of Psychiatry at King's College in collaboration with the MS Society UK. The study is being conducted as part of the Principal Investigator (Anthony Harrison's) doctoral studies in conjunction with Lead Investigators Professor Rona Moss-Morris and Professor Lance McCracken, and Katherine Jones, an undergraduate student completing her science degree. Anthony and Katherine are being supervised by the Lead Investigators with all aspects of the project.

What is the purpose of the study?
Research has shown that people with MS experience different kinds of pain, and that coping with the emotions, lifestyle changes and other problems associated with pain can be challenging. Many people with MS pain experience periods of feeling frustrated or angry, down, distressed and/or anxious. In this small pilot study we would like to find out whether a guided self-help programme based on both Cognitive behavioural Therapy (CBT) and Acceptance and Commitment Therapy (ACT) could help people with MS-related pain and how to make this programme more relevant to your needs in the future.

What is the therapy that is being tested?
The guided self-help programme will test a combination of techniques from both traditional Cognitive Behavioural Therapy (CBT) and Acceptance and Commitment Therapy (ACT). With Anthony's support, participants will be encouraged to look at the ways that their thoughts, feelings, behaviours and physiology all interact and influence how MS pain affects their lives. The treatment is quite structured and different topics will be covered in different sessions (e.g. relationships with others or

related symptoms). Participants will also be expected to set goals to achieve. Participants will have small tasks or "homework" to do in between the sessions.

Why was I invited to take part?
Four to six people with MS-related pain will take part in this project. You have been approached because you took part in our previous pain experience in Multiple Sclerosis (PEMS) survey study (REC No: 13/LO/1429). In your completed PEMS survey you indicated that you experience some form of MS-related pain for longer than six months and expressed an interest in us contacting you about future MS pain studies. This invitation to take part does not mean that your doctors think you are having particular difficulties or are having problems coping. We are inviting people to take part regardless of whether they feel distressed, down or anxious at the moment.

Can I take part in this study?
You will take part in a screening session over the telephone where Anthony will confirm your eligibility to take part.

Our criteria request you are:

- 18 years-of-age or over
- Have a definite diagnosis of any subtype of MS and any level of disability
- Have any form of pain starting either at the time of MS diagnosis or suspected diagnosis, or after the diagnosis of MS.
- On a 10-point scale of 1 ('No pain') to 10 ('Pain as bad as you can imagine'), rate your pain severity as '4' or greater.
- On a 10-point scale of 1 ('Does not interfere) to 10 ('Completely interferes'), rate your pain severity as '4' or greater.
- If you are taking pain medications you must have been on the medication for at least three months and intend to continue for the duration of the study.
- Have not received any formal training in CBT or ACT. This is because we would like to see whether our programme is helpful and we won't be able to do so if you have completed similar programmes before or if you are receiving additional psychological help.
- Not currently receiving any other psychological treatment.
- Are willing not to try any new psychological treatments during the duration of the study. However, if new treatments are required, they will be allowed and we ask that you inform Anthony
- You have a telephone or Skype internet access

Unfortunately, you won't be able to take part in this study if you have severe mental problems or substance misuse. Also, if you are highly distressed, this type of intervention might not be the most appropriate for you. We will discuss these issues with you over the phone before the start of the programme and we may suggest an alternative approach for you.

Do I have to take part?
No. It is up to you to decide whether or not to take part after reading this information sheet. If you agree to take part, you will be given this information sheet to keep and be asked to sign a consent form at the end of this document. You are still free to leave the study at any stage without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part? What do I have to do?
The research project will involve an 8-week guided self-help programme for MS pain. The sessions of the guided self-help MS pain programme will take place once a week for eight weeks, with each session lasting about an hour. Anthony will facilitate the programme and distribute the booklets and assistive media you will need. Around three sessions will be scheduled during the 8 weeks to help guide you through the programme and answer any questions you have. Your Skype and/or telephone

sessions with Anthony will need to be undertaken in a private location where you can talk undisturbed. We ask that you complete the remaining five sessions independently. However, Anthony will be contactable throughout the programme if you have any questions. As part of the programme we will ask you to practice new skills regularly using the booklet and CDs we will provide you with.

We will ask you to fill in a short questionnaire ratings about your pain and how you are thinking and feeling every four days over the 16 week period: during the month before the programme begins, during the eight week programme and then one month after the programme has finished. The questionnaire ratings will take between 5 to 10 minutes to complete. A researcher, Ms Katherine Jones, independent of Mr Harrison, who will deliver the treatment, will send these to you every four weeks by post in a booklet format so you can complete them at home. Alternatively, you can complete the questionnaires online if you prefer. Ms Jones will also send you regular reminder text messages or emails to remind you to complete the questionnaire ratings every four days. You will be asked to refrain from taking part in any other CBT or ACT course during this period.

We will record all telephone or Skype sessions so that we can check that Anthony is conducting the sessions in exactly the way that was planned. The recordings will be stored for supervision purposes until the end of the programme, at which point they will be safely destroyed.

At the end of the treatment programme we will interview all participants about their experiences and views about the programme sessions. If you agree to take part Ms Katherine Jones will contact you and arrange a convenient time with you to conduct an informal interview over the telephone for about one hour. Ms Jones will not be involved in the delivery of the programme. Ms Jones will tape-record your interview and transcribe it omitting your name or any other identifiable information before giving the transcripts to the research team to study it at a later date. Katherine will transcribe your interview within two months, at which stage we will securely destroy the interview recordings. If you want to take part in the self-help programme but do not want to do this interview you do not have to. You can also change your mind if you agree to do the interview but decide you no longer want to at a later date.

Expenses and benefits
You will be given a £80 if you complete the 8-week programme and all the associated questionnaire ratings. If you complete only one session for instance we will pay you £10. Unfortunately, we cannot compensate you if you withdraw prior to attending any sessions. There will be no cost to you for the self-help materials or initial session. The researchers will make and pay for the telephone calls for your treatment sessions. We will either contact you via telephone or use Skype (a free online application), depending on your preferences. The questionnaires and any telephone headset equipment you need will be mailed to you Ms Jones and delivery will be arranged and will contain pre-paid envelopes for their return to us.

What are the alternatives for treatment?
This treatment is in addition to any current NHS treatments you are receiving for your pain including pain medication and physiotherapy. You will not be required to stop these treatments, although we request that you do not start other new treatment whilst taking part in this study. Currently there is no other readily available NHS pain management programme specifically for people with MS. However, there are pain self-help guides for more general pain problems which are available for purchase. Some hospital trusts also run a specialised pain service where people can be referred to learn pain management strategies. However, these are not specific to MS and often focus on people with a primary pain problem (i.e. pain that is not secondary to a disease)

Do I need any special equipment to take part?
You will need to have a working telephone or a computer with an Internet connection that has Skype software (including a headset and camera, as preferred). Unfortunately, we can only provide telephone headsets.

What are the possible disadvantages and risks of taking part?
The main disadvantage of taking part is simply the time and effort it will take. It is also possible that exploring issues to do with your pain may be difficult for you. However, CBT and ACT approaches are designed to help people to feel better and we don't expect that people will feel any worse as a result of taking part. If, through taking part in the research, it becomes clear that you are having any major difficulties (e.g. with depression) we will refer you to further sources of support.

What are the side effects of any treatment received when taking part?
You are being offered a self-management programme with elements of talking therapy. It is very unlikely that there will be any side-effects.

What are the possible benefits of taking part?
We cannot promise the study will help you. However, the evidence so far shows that both CBT and ACT programmes are helpful for people with chronic pain conditions. Further the information we get will help us make the programme more relevant to the needs of people with MS-related pain. At the conclusion of the project, we will send you a newsletter describing the major findings and alerting you to any research publications we have generated from the project.

What happens when the research study stops?
The information we will gain from this project will help us to decide whether the intervention is helpful for people with MS-related pain and will help us find out ways to make the programme more helpful. However, the programme will not be available after the eight-week treatment period has finished. Even if the results of this study show that the programme was very effective it will not necessarily be available in the foreseeable future at your local NHS hospital. However, you can keep the assisted self-help guide and media at the end of the study.

What if there is a problem?
It is up to you to decide whether to take part or not. If you decide to take part you are still free to withdraw at any time and without giving a reason. If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact: Anthony Harrison (Principle Investigator) (anthony.harrison@kcl.ac.uk or tel. 02071889324) or Rona Moss-Morris (Chief Investigator) (rona.moss-morris@kcl.ac.uk or tel. 020 7188 0180). If you have a complaint, you should talk to your research doctor who will do their best to answer your questions. If you remain unhappy, you may be able to make a formal complaint through the NHS complaints procedure. Details can be obtained through the Guy's and St Thomas' Patient Advisory Liaison Service (PALS) on 0207 1887188 or email pals@gstt.nhs.uk, address: PALS, KIC, Ground floor, north wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH .

This trial is sponsored by King's College London. The sponsor will at all times maintain adequate insurance in relation to the study independently. Kings College London, through its own professional indemnity (Clinical Trials) and no fault compensation and the Trust having a duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of clinical negligence by its employees, brought by or on behalf of a study patient.

Will my taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2
Information you need to know if you still want to take part

What will happen if I don't want to carry on with the study?
You are free to withdraw from the study at any time without having to give a reason even if you decide to take part initially. However, we will need to use the data you have provided so far so that we can analyse the results from the study accurately. We will remove any information that can reveal your identity.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researcher who will do his best to answer your questions (Anthony Harrison on 07936 448 926 or anthony.harrison@kcl.ac.uk).

Will my part in this study be kept confidential?
Yes. The procedures for handling, processing, storing and destroying data are compliant with the Data Protection Act 1998. Data about you will be linked to a number rather than your name in order to maintain anonymity. Information about you will be stored securely and will be available only to members of the research team. It will be used only for the purposes of the current study. Data from this study will be retained until the study has been written up for publication (not more than 5 years) and subsequently disposed of securely.

What will happen to the results of the research study?
The results will be used to help the researchers to decide whether the guided self-help programme is useful for people with MS-related pain and identify possible ways to make it more relevant to their needs. The study will also be written up for publication in scientific journals and may be presented at scientific conferences. If you would like to know the results you can be provided with a summary sheet.

Who is organising and funding the research?
The research is being organised and conducted by researchers from King's College London, UK and it is funded by the MS Society, UK.

Who has reviewed the study?
This study has been reviewed and given favourable opinion by the Camden & Islington NHS Ethics Committee (Ref: 14/LO/1909) and by a patient and public involvement members at the UK Multiple Sclerosis Society.

What if I have questions about the project?
If you would like to discuss your potential involvement in this research further please contact:

Name: Mr Anthony Harrison **Job title:** Principal Investigator (Doctoral Student)
Telephone number: 07936 448 926 **Email address:** anthony.harrison@kcl.ac.uk
Address: Department of Health Psychology, Institute of Psychiatry, Kings College London, 5th Floor Bermondsey Wing, Guys Campus, London SE1 9RT
Please retain this information sheet.
If, after discussing the research with us, you decide that you wish to participate we will ask you to complete and return a consent form. You will get a copy of the consent form to keep.

Appendix S. Chapter 6 Case Series: Consent Form

KING'S College LONDON

University of London

Guy's and St Thomas' NHS

NHS Foundation Trust

CONSENT FORM

Title of Project: **Guided cognitive behavioural selF-help Treatment for multiple sclerosis pain (GIFT Study) (REC REF: 14/LO/1909)**

Name of Researchers: Mr Anthony Harrison, Ms Katherine Jones, Professor Rona Moss-Morris, Professor Lance McCracken

Please initial the box at the end of each statement to confirm

1. I confirm that I have read and understand the information sheet dated **10.11.2014 (version 1)** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that data collected during the study, may be looked at by individuals from King's College London, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I give permission for the sessions I take part to be audiotaped. ☐

5. I agree to my GP being informed of my participation in the study. ☐

6. I agree to take part in the above study. ☐

OPTIONAL EXTRA INTERVIEW
(You can do the rest of the project without doing this)

1. I agree to take part in an interview about my experiences of therapy at the end of my treatment. ☐
2. I give permission for the interview I take part to be audiotaped. ☐
3. I understand that when the research is published it may include direct quotations from my interview but that I will not be identified as an individual. ☐

_____ _____ _____

Name of Participant Date Signature

CONTACT DETAILS

Address:_____

_____

Post code _____

Telephone Number_____

Email:_____

PARTICIPANT ID: _____ (To be stored separately to ICF)

GP CONTACT DETAILS

Doctor:
_____

Address:
_____

_____

Post code _____

Appendix T. Chapter 6 Case Series: Validated Screening and Pre-Baseline Questionnaires

Brief Pain Inventory (BPI) (adapted single-item pain severity and interference numerical rating scales) (Cleeland & Ryan, 1994)

1. Please rate your pain by circling the one number that best describes your pain on average <u>today</u>										
0 No Pain	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Pain as bad as you can imagine**
2. Circle the one number that describes how much pain has <u>interfered</u> with your day:										
0 Does Not Interfere	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Completely Interferes**

Telephone Interview for Cognitive Status (TICS-M) (Brandt et al., 1993)

	Score '1' for each correct answer and '0' if incorrect	
Orientation		
1. (i) What day of the week is it?	Day	
(ii) What is today's date?	Date Month Year	
(iii) What season are we in?	Season	
2. What is your age?	Age	
3. What is your telephone number? (Code+number)		
Registration/Free Recall		
4. I'm going to read you a list of 10 words. Please listen carefully and try to remember Cabin & them. When I am done, tell me as many as you can in any order. Ready? Now, tell me all the words you can remember	Cabin Pipe Elephant Chest Silk Theatre Watch Whip Pillow Giant	
Attention/Calculation		
5. Please take 7 away from 100 Now continue to take 7 away from what you have left over until I ask you to stop.	93 86 79 72 65	
6. Please count backwards from 20 to 1	No mistakes	
Comprehension, Semantic and Recent Memory		
7. What do people usually use to cut paper?	Scissors	
8. What is the prickly green plant found in the desert?	Cactus	
9. Who is the reigning monarch now?	E, QE, QE2	
10. Who is the Prime Minister now?	Correct surname	
11. What is the opposite of east?	West	
Language/Repetition		
12. Please say this 'Methodist Episcopal'	Exactly right	
Delayed Recall		
13. Please repeat the list of 10 words I read earlier	Cabin Pipe Elephant Chest Silk Theatre Watch Whip Pillow Giant	
		maximum of 39

Self-report EDSS (EDSS-S) (Bowen et al., 2001)

WALKING DISTANCES

We would like to know how well your body functions on an average day, not your worst days and not your best days. Please tick the box that most closely matches your abilities.**

On an average day I can:

☐ Walk more than 500 metres (about 530 yards) without stopping to rest.
(This is approximately 5 football field lengths.)
I would need ☐ no help ☐ a cane ☐ two canes ☐ a walker

☐ Walk 300 metres (about 350 yards) without stopping to rest.
(This is approximately 3 football field lengths.)
I would need ☐ no help ☐ a cane ☐ two canes ☐ a walker

☐ Walk 200 metres (about 200 yards) without stopping to rest.
(This is approximately 2 football field lengths.)
I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

☐ Walk 100 metres (about 100 yards) without stopping to rest.
(This is approximately 1 football field length.)
I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

☐ Walk 20 metres (about 60 feet) without stopping to rest.
I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

☐ Walk 5 metres (about 15 feet) without stopping to rest
I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

☐ Walk a few steps.
I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

☐ Use a wheelchair

If you use a wheelchair please **tick one** of the following 4 statements:

1. ☐ On an average day, I can bear my weight with my legs (stand up and move) and get myself from one chair to another.
2. ☐ On an average day, I can bear my weight (with the strength in my arms) and lift myself from one chair to another.
3. ☐ On an average day, I cannot bear any weight or get myself from one chair to another.
4. ☐ On an average day, I cannot sit up in a chair.

STRENGTH

When answering the following questions, please think about an average day for you (not a particularly good, or bad day) then think of the "best" part of that day. (Maybe the best part of your day is in the morning, or maybe later, after you have moved around a bit.)

On an **average** day, at my **best**, my strength is:

	The same as before I had MS	Almost the same as before I had MS	Can barely raise limb in the air	Can move limb, but not raise it in the air	Cannot move limb at all
Right arm	☐	☐	☐	☐	☐
Left arm	☐	☐	☐	☐	☐
Right leg	☐	☐	☐	☐	☐
Left leg	☐	☐	☐	☐	☐

COORDINATION

On an average day, at my best, my coordination:

	The same as before I had MS	Almost the same as before I had MS	Interferes with some movements, though I can eventually complete them without help	I must get help, use a mechanical device, or brace the limb to complete movements	Prevents me from completing movements even with help.
Right arm	☐	☐	☐	☐	☐
Left arm	☐	☐	☐	☐	☐
Right leg	☐	☐	☐	☐	☐
Left leg	☐	☐	☐	☐	☐

SENSATION

For touch, pain, cold, or heat, please mark the appropriate box in the table below. **Use the worst – the one that has lost the most sensitivity – of the four sensations** (touch, pain, cold, or heat) to answer each question. Please think of an **average** day.
(For example: your left hand has very little sensitivity to pain, mild sensitivity to touch, and normal for heat and cold, then you would mark “can feel very little” on the line for left hand.)

	Same as before I had MS	Mild loss of sensation	Moderate loss of sensation	Can feel very little
Right hand	☐	☐	☐	☐
Right arm	☐	☐	☐	☐
Left hand	☐	☐	☐	☐
Left arm	☐	☐	☐	☐
Right foot	☐	☐	☐	☐
Left foot	☐	☐	☐	☐
Left leg	☐	☐	☐	☐

BLADDER

On an **average** day, I have:

Yes	No	
☐	☐	A normal bladder
☐	☐	Urgency (once I need to go I have a hard time holding it)
☐	☐	Hesitancy (I feel I need to go but nothing happens)
☐	☐	Accidents (incontinence) occasionally but once a week or less
☐	☐	Accidents (incontinence) twice a week or more, but less than daily
☐	☐	Accidents (incontinence) daily
☐	☐	Use self-catheterization
☐	☐	Use continuous catheter (indwelling or condom catheter)

VISION

1. Which line is the smallest that you can read (you can use glasses if needed).

Left eye only	Right eye only	Both eyes together	
☐	☐	☐	937826
☐	☐	☐	428365
☐	☐	☐	374258
☐	☐	☐	4 2 8 3 6 5
☐	☐	☐	Cannot read any of the lines above

2. I see double (two things, where there is really only one)

☐ Never ☐ About once a week ☐ Almost daily
☐ Constantly

3. On an average day, my eye movements are unsteady
☐ Never ☐ Only when looking to the side ☐ All the time

SPEECH

On an average day, my speech is:
☐ The same as before I had MS
☐ Slightly Slurred
☐ Moderately Slurred
☐ Severely Slurred

SWALLOWING

On an average day, my swallowing is:
☐ Normal
☐ Occasional choking
☐ Unable to swallow

THINKING

Although some people may wish to consider thinking and memory separately, we need you to combine them and tick one box below.

On an average day, my thinking and memory is:
☐ Is the same as before I had MS
☐ Is almost the same as before I had MS
☐ Occasionally causes a problem in my daily life
☐ Frequently causes a problem in my daily life
☐ Others have to help me manage my affairs

Appendix U. Chapter 6 Case Series: Validated Measures (collected every four days)

Brief Pain Inventory (BPI) (adapted single-item pain severity and interference numerical rating scales) (Cleeland & Ryan, 1994)

1. Please rate your pain by circling the one number that best describes your pain on average today										
0 No Pain	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Pain as bad as you can imagine**
3. Circle the one number that describes how much pain has interfered with your day:										
0 Does Not Interfere	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Completely Interferes**

Brief Illness/Pain Perceptions Questionnaire (BIPQ)
(Broadbent et al., 2006)

For the following questions, please select the number that best corresponds to your views:

How much does your pain affect your life?

0	1	2	3	4	5	6	7	8	9	10
No affect at all										Severely affects my life

How long do you think your pain will continue?

0	1	2	3	4	5	6	7	8	9	10
A very short time										Forever

How much control do you feel you have over your pain?

0	1	2	3	4	5	6	7	8	9	10
Absolutely no control										Extreme amount of control

How much does your pain affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?

0	1	2	3	4	5	6	7	8	9	10
not at all affected emotionally										extremely affected emotionally

Validated Chronic Pain Acceptance Questionnaire-8 items (CPAQ-8)
(Fish et al., 2010)

Below you will find a list of statements. Please rate the truth of each statement as it applies to you by circling a number.

Use the following rating scale to make your choices (*Please tick one grey box for each statement.)*

1. I am getting on with the business of living no matter what my level of pain is.

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

2. Keeping my pain level under control takes first priority whenever I'm doing something.

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

3. Although things have changed, I am living a normal life despite my chronic pain.

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

4. Before I can make any serious plans, I have to get some control over my pain.

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

5. I lead a full life even though I have chronic pain.

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

6. When my pain increases, I can still take care of my responsibilities.

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

7. I avoid putting myself in situations where my pain might increase.

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

8. My worries and fears about what pain will do to me are true

Never True	Very Rarely true	Seldom True	Sometimes True	Often True	Almost Always True	Always True

Avoidance-Endurance Questionnaire (AEQ) Avoidance of Social Activities Scale (ASAS) (adapted for pain overall rather than for mild or moderate) (Hasenbring et al., 2009)

When in pain…

0 Never True	1 Very Rarely true	2 Seldom True	3 Sometimes True	4 Often True	5 Almost Always True	6 Always True

1. I avoid visiting friends	0 1 2 3 4 5 6
2. I cancel private appointments	0 1 2 3 4 5 6
3. I cancel a visit to an event	0 1 2 3 4 5 6
4. I break-off a meeting with friends	0 1 2 3 4 5 6
5. I call my guests to cancel an invitation	0 1 2 3 4 5 6
6. I avoid other people's company	0 1 2 3 4 5 6

Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995)

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

When I'm in pain… (*Please tick one grey box for each statement.)*

1. I worry all the time about whether the pain will end.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

2. I feel I can't go on.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

3. It's terrible and I think it's never going to get any better.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

4. It's awful and I feel that it overwhelms me.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

5. I feel I can't stand it anymore.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

6. I become afraid that the pain will get worse.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

7. I keep thinking of other painful events.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

8. I anxiously want the pain to go away.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

9. I can't seem to keep it out of my mind.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

10. I keep thinking about how much it hurts.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

11. I keep thinking about how badly I want the pain to stop.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

12. There's nothing I can do to reduce the intensity of the pain.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

13. I wonder whether something serious may happen.

Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

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